Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/043145

International filing date: 22 December 2004 (22.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/532,248
Filing date: 23 December 2003 (23.12.2003)

Date of receipt at the International Bureau: 31 January 2005 (31.01.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

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APPLICATION NUMBER: ***60/532,248***
FILING DATE: ***December 23, 2003***
RELATED PCT APPLICATION NUMBER: ***PCT/US04/43145***

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

15535 U.S. PTO
60/532248
122303

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☐ *Additional inventors are being named on the_____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (280 characters max)

CO-ADMINISTRATION OF DOPAMINE RECEPTOR BINDING COMPOUNDS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* **52**

☒ Drawing(s) *Number of Sheets* **4**

☐ Application Data Sheet. See 37 CFR 1.76

☐ CD(s), Number

☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☒ Applicant claims small entity status. See 37 CFR 1.27.

☒ A check or money order is enclosed to cover the filing fees

☒ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number **10-0435**

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: ________________

Respectfully submitted,

SIGNATURE Rebecca Ball

Date **12/23/2003**

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REGISTRATION NO. *(if appropriate)* **46,535**

TELEPHONE **317-231-7511**

Docket Number: **30152-74051**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group:	Unknown
Attorney Docket:	30152-74051
Applicant:	Prabhavathi Fernandes et al.
Invention:	**Co-Administration Of Dopamine Receptor Binding Compounds**
Serial No:	Unknown
Filed:	December 23, 2003

CERTIFICATE UNDER 37 C.F.R. § 1.10

Mail Stop Provisional Application
Commissioner For Patents
P.O. Box 1450
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Express Mail label number: EV 404 966 483 US

Date of deposit: December 23, 2003

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Respectfully submitted,

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PROVISIONAL PATENT APPLICATION

of

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for

CO-ADMINISTRATION OF DOPAMINE RECEPTOR BINDING COMPOUNDS

Attorney Docket 30152-74051

CO-ADMINISTRATION OF DOPAMINE-RECEPTOR BINDING COMPOUNDS

FIELD OF THE INVENTION

The invention relates to a method and composition for treating a patient having a neurological disorder by co-administration of dopamine receptor-binding compounds to the patient. More particularly, the invention relates to a method and composition for co-administration of a D_1 dopamine receptor agonist and a D_2 dopamine receptor antagonist for treating a patient having a neurological disorder.

BACKGROUND

It is generally accepted that there are at least two pharmacological subtypes of dopamine receptors (the D_1 and D_2 receptor subtypes), each consisting of several molecular forms. D_1 receptors preferentially recognize the phenyltetrahydrobenzazepines and generally lead to stimulation of the enzyme adenylate cyclase, whereas D_2 receptors recognize the butyrophenones and benzamides and often are coupled negatively to adenylate cyclase, or are not coupled at all to this enzyme. It is now known that at least five dopamine receptor genes encode the D_1, D_2, D_3, D_4 and D_5 receptor isoforms or subtypes. The traditional classification of dopamine receptor subtypes, however, remains useful with the D_1-like class comprising the D_1 (D_{1A}) and the D_5 (D_{1B}) receptor subtypes, whereas the D_2-like class consists of the D_2, D_3 and D_4 receptor subtypes.

The physiological activities associated with the interaction of dopamine agonists with these receptor subtypes are not fully understood. As the effects caused by association of selective ligands with specific receptor subtypes become better resolved, researchers will be much better positioned to design drugs targeting specific disease states or disorders. Dopamine receptor agonists are of therapeutic interest for a variety of reasons. For example, it has been hypothesized that excessive stimulation of D_2 dopamine receptor subtypes may be linked to schizophrenia. Additionally, it is generally recognized that either excessive or insufficient dopaminergic activity in the central nervous system can cause hypertension, narcolepsy, and other behavioral, neurological, physiological, and movement disorders, including Parkinson's disease.

Patients with schizophrenia and other neurological disorders, such as psychosis, bipolar disorder, anxiety states, and depression in combination with psychotic episodes, can have both "positive" symptoms (*e.g.*, delusions, hallucinations, impaired cognitive function, and agitation), as well as "negative" symptoms (*e.g.*, emotional unresponsiveness), and impaired cognitive function. Patients with these psychotic signs and symptoms can be treated with drugs that fall into the general classes of typical antipsychotic drugs and atypical antipsychotic drugs. The typical antipsychotic agents include phenothiazines, butyrophenones, and other non-phenothiazines such as loxapine and molindone. The atypical antipsychotic agents include the clozapine-like drugs (*e.g.*, clozapine, olanzepine, quetiapine, ziprasidone, etc.) as well as several others that include risperidone, aripiprazole, and amisulpiride, among others. Whereas both of these typical and atypical antipsychotic agents are useful for treating the positive symptoms of the neurological disorders described herein, patients may not find total relief from the negative symptoms that may accompany these antipsychotic agents.

SUMMARY

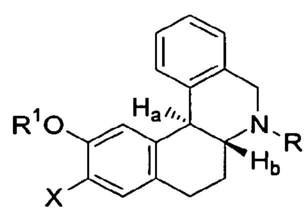
The compounds useful in the method and composition described herein for co-administration of dopamine receptor-binding compounds are 1) partial or full D_1 receptor agonists, and 2) D_2 receptor antagonists. In accordance with the method and composition described herein, an effective amount of a partial or full D_1 receptor agonist can be co-administered to a patient having a neurological disorder along with an effective amount of a D_2 receptor antagonist to reduce the symptoms of the neurological disorder (*e.g.*, to reduce both the positive and the negative symptoms of neurological disorders such as schizophrenia, the D_1 agonist being used to reduce the negative symptoms). The partial or full D_1 receptor agonist and the D_2 receptor antagonist can be administered to the patient having the neurological disorder either in the same or in a different composition or compositions.

In one embodiment, a method for treating a patient having a neurological disorder is provided. The method comprises the steps of administering to the patient an effective amount of a partial or full D_1 dopamine receptor agonist where the dopamine agonist is illustratively a compound selected from the group consisting of hexahydrobenzophenanthridines, hexahydrothienophenanthridines,

phenylbenzodiazepines, chromenoisoquinolines, naphthoisoquinolines, and pharmaceutically acceptable salts thereof, including combinations of the foregoing, and administering to the patient an effective amount of a D_2 dopamine receptor antagonist.

In one embodiment, the partial or full D_1 dopamine receptor agonist can be selective for a D_1 dopamine receptor subtype. In another embodiment, the partial or full D_1 dopamine receptor agonist can exhibit activity at both the D_1 and D_2 dopamine receptor subtypes. For example, the full D_1 dopamine receptor agonist can be about equally selective for the D_1 and D_2 dopamine receptor subtypes. In another embodiment, the partial or full D_1 dopamine receptor agonist can be selective for a D_1 dopamine receptor or receptor subtype associated with a particular tissue. In another embodiment, the partial or full D_1 dopamine receptor agonist can be selective for a D_1 dopamine receptor or receptor subtype capable of exhibiting functional selectivity with the D_1 dopamine receptor agonist.

In one embodiment, the dopamine receptor agonist can be a compound having Formula **I**:



(I)

wherein:

H_a and H_b are *trans* across the ring fusion bond;

R is hydrogen or C_1-C_4 alkyl;

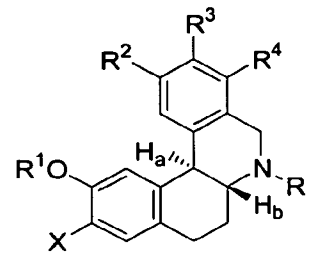
R^1 is hydrogen, acyl, such as benzoyl, pivaloyl, and the like, or an optionally substituted phenyl protecting group; and

X is hydrogen, fluoro, chloro, bromo, or iodo, or

X is a group having the formula $-OR^2$ wherein R^2 is hydrogen, C_1-C_4 alkyl, acyl, such as benzoyl, pivaloyl, and the like, or an optionally substituted phenyl protecting group; or the groups R^1 and R^2 are taken together to form a divalent radical having the formula $-CH_2-$ or $-(CH_2)_2-$;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the dopamine receptor agonist can be a compound having Formula **II**:



(II)

wherein:

H_a and H_b are *trans* across the ring fusion bond;

R is hydrogen or C_1-C_4 alkyl;

R^1 is hydrogen, acyl, such as benzoyl, pivaloyl, and the like, or an optionally substituted phenyl protecting group;

X is hydrogen, fluoro, chloro, bromo, or iodo, or

X is a group having the formula $-OR^5$ wherein R^5 is hydrogen, C_1-C_4 alkyl, acyl, such as benzoyl, pivaloyl, and the like, or an optionally substituted phenyl protecting group; or the groups R^1 and R^5 are taken together to form a divalent radical having the formula $-CH_2-$ or $-(CH_2)_2-$; and

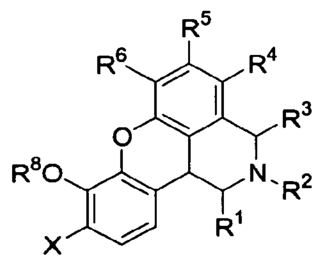
R^2, R^3, and R^4 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, phenyl, fluoro, chloro, bromo, iodo, and a group $-OR^6$ wherein R^6 is hydrogen, acyl, such as benzoyl, pivaloyl, and the like, or an optionally substituted phenyl protecting group,

or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the dopamine receptor agonist can be a compound having Formula **II**, wherein R, R^1, R^2, R^3, R^4, and X are as described above, and where at least one of R^2, R^3, and R^4 is other than hydrogen;

or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the dopamine receptor agonist can be a compound having Formula **III**:



(III)

wherein:

R^1, R^2, and R^3 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, and C_2-C_4 alkenyl;

R^4, R^5, and R^6 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, phenyl, halo, and a group having the formula -OR, where R is hydrogen, acyl, such as benzoyl, pivaloyl, and the like, or an optionally substituted phenyl protecting group;

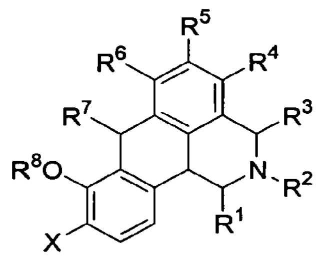
R^8 is hydrogen, C_1-C_4 alkyl, acyl, or an optionally substituted phenyl protecting group;

X is hydrogen, fluoro, chloro, bromo, or iodo, or

X is a group having the formula -OR^9, where R^9 is hydrogen, C_1-C_4 alkyl, acyl, or an optionally substituted phenyl protecting group; orthe groups R^8 and R^9 are taken together to form a divalent group having the formula -CH_2- or -$(CH_2)_2$-;

or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the dopamine receptor agonist can be a compound having Formula **IV**:



(IV)

wherein:

R^1, R^2, and R^3 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, and C_2-C_4 alkenyl;

R^4, R^5, and R^6 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, phenyl, halogen, and a group having the formula -OR^6, where R^6 is as defined above in Formula **II**;

R^7 is selected from the group consisting of hydrogen, hydroxy, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkoxy, and C_1-C_4 alkylthio;

R^8 is hydrogen, C_1-C_4 alkyl, acyl, or an optionally substituted phenyl protecting group;

X is hydrogen, fluoro, chloro, bromo, or iodo, or

X is a group having the formula $-OR^9$, where R^9 is hydrogen, C_1-C_4 alkyl, acyl, or an optionally substituted phenyl protecting group; orthe groups R^8 and R^9 are taken together to form a divalent group having the formula $-CH_2-$ or $-(CH_2)_2-$;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the D_2 dopamine receptor antagonist is an antipsychotic agent, and is illustratively selected from the typical and atypical families of antipsychotic agents. In one aspect, the typical antipsychotic agents include phenothiazines and non-phenothiazines such as loxapine, molindone, and the like. In another aspect, the atypical antipsychotic agents include the clozapine-like agents, and others, including aripiprazole, risperidone, amisulpiride, sertindole, and the like. Phenothiazines include, but are not limited to chlorpromazine, fluphenazine, mesoridazine, perphenazine, prochlorperazine, thioridazine, and trifluoperazine. Non-phenothiazines include, but are not limited to haloperidol, pimozide, and thiothixene. Clozapine-like agents include, but are not limited to olanzapine, clozapine, quetiapine, and ziprasidone. It is appreciated that other typical and atypical antipsychotic agents may be used in the methods and compositions described herein. It is also appreciated that various combinations of typical and atypical antipsychotic agents may be used in the methods and compositions described herein.

In one embodiment, a method is described wherein the D_1 dopamine receptor agonist and the D_2 dopamine receptor antagonist are administered to the patient in the same composition, and, in another embodiment, the D_1 dopamine receptor agonist and the D_2 dopamine receptor antagonist are administered to the patient in different compositions.

In still another embodiment, a pharmaceutical composition is described. The composition comprises a partial or full D_1 dopamine receptor agonist wherein the dopamine agonist is illustratively a compound selected from the group consisting of hexahydrobenzophenanthridines, hexahydrothienophenanthridines, phenylbenzodiazepines, chromenoisoquinolines, naphthoisoquinolines, and pharmaceutically acceptable salts thereof, including combinations of the foregoing, and a D_2 dopamine receptor antagonist.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates the chemical conversions detailed in Examples 1-4 for preparation of dihydrexidine and other hexahydrobenzo[*a*]phenanthridine compounds having formulae **I** and **II**: (a) 1. Benzylamine, H_2O; 2. ArCOCl, Et_3N; (b) hν; (c) BH_3·THF; (d) H_2, 10% Pd/C; (e) 48% HBr, reflux.

Fig. 2 illustrates the chemical conversions detailed in Examples 7-8 for preparation of dinoxyline and other chromeno[4,3,2-*de*]isoquinoline compounds having formula **III**: (a) 1. NaH, THF; 2. CH_3OCH_2Cl, 0 °C → r.t.; 82%; (b) 1. *n*-BuLi; 2. -78 °C → r.t.; 76%; (c) KNO_3, H_2SO_4; 89%; (d) $Pd(Ph_3)_4$, KOH, $Bu_4N^+Cl^-$, H_2O, DME, reflux; (e) TsOH·H_2O, MeOH; 98%; (f) DMF, K_2CO_3, 80 °C; 86%; (g) PtO_2, AcOH, HCl, H_2; 99%; (h) R-L, K_2CO_3, acetone; (i) BBr_3, CH_2Cl_2, -78 °C → r.t.; 72%.

Fig. 3 illustrates the chemical conversions detailed in Example 9 for preparation of 2-methyl-2,3-dihydro-4(1*H*)-isoquinolone, an intermediate in the synthesis of dinapsoline, from ethyl 2-toluate: (a) NBS (N-bromosuccinimide, benzoylperoxide, CCl_4, reflux; (b) sarcosine ethylester HCl, K_2CO_3, acetone; (c) 1. NaOEt, EtOH, reflux, 2. HCl, reflux.

Fig. 4 illustrates the chemical conversions detailed in Example 10 for preparation of dinapsoline and other naphthoisoquinolines from 2,3-dimethoxy-*N,N'*-diethylbenzamide: (a) 1. *sec*-butyllithium, TMEDA, Et_2O, -78°C, 2. Compound **20**, 3. TsOH, toluene, reflux; (b) 1. 1-chloroethylchloroformate, $(CH_2Cl)_2$, 2. CH_3OH; (c) TsCl, Et_3N; (d) H_2, Pd/C, HOAc; (e) BH_3·THF; (f) conc. H_2SO_4, -40 °C to -5 °C; (g) Na/Hg, CH_3OH, Na_2HPO_4; (h)BBr_3, CH_2Cl_2.

DETAILED DESCRIPTION

The compounds useful in the method and composition described herein for co-administration of dopamine receptor-binding compounds are 1) partial and full D_1 agonists with biological activities ranging from compounds with selective D_1 receptor agonist activity to compounds with potent activities affecting both D_1 and D_2 dopamine receptor subtypes, and 2) D_2 receptor antagonists. In accordance with the method and composition described herein, an effective amount of a partial or full D_1 receptor agonist can be co-administered to a patient having a neurological disorder along with an effective amount of a D_2 receptor antagonist to reduce the symptoms of

the neurological disorder (*e.g.*, to reduce both the positive and the negative symptoms of neurological disorders such as schizophrenia). The partial or full D_1 receptor agonist and the D_2 receptor antagonist can be administered to the patient having the neurological disorder either in the same or in a different composition or compositions.

Exemplary neurological disorders that can be treated with the method and composition described herein include such neurological disorders as schizophrenia, schizophreniform disorder, schizoaffective disorders, including those characterized by the occurrence of a depressive episode during the period of illness, bipolar disorder, depression in combination with psychotic episodes, and other disorders that include a psychosis. The types of schizophrenia that may be treated include Paranoid Type Schizophrenia, Disorganized Type Schizophrenia, Catatonic Type Schizophrenia, Undifferentiated Type Schizophrenia, Residual Type Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Schizoaffective Disorder of the Depressive Type, and Major Depressive Disorder with Psychotic Features. Typically, the neurological disorders that can be treated have both "positive" symptoms (*e.g.*, delusions, hallucinations, impaired cognitive function, and agitation) and "negative" symptoms (*e.g.*, emotional unresponsiveness).

Other disorders that have a psychotic component and a depressive component that can be treated include premenstrual syndrome, anorexia nervosa, substance abuse, head injury, and mental retardation. Additionally, endocrine conditions, metabolic conditions, fluid or electrolyte imbalances, hepatic or renal diseases, and autoimmune disorders with central nervous system involvement which have a psychotic component and a depressive component may be treated with the composition and method described herein.

The D_2 dopamine receptor antagonists that can be used in accordance with the method and composition described herein include typical or atypical families of antipsychotic agents. In one aspect, the typical antipsychotic agents include phenothiazines and non-phenothiazines such as loxapine, molindone, and the like. In another aspect, the atypical antipsychotic agents include the clozapine-like agents, and others, including aripiprazole, risperidone, amisulpiride, sertindole, and the like. Phenothiazines include, but are not limited to chlorpromazine, fluphenazine, mesoridazine, perphenazine, prochlorperazine, thioridazine, and trifluoperazine. Non-phenothiazines include, but are not limited to haloperidol, pimozide, and thiothixene.

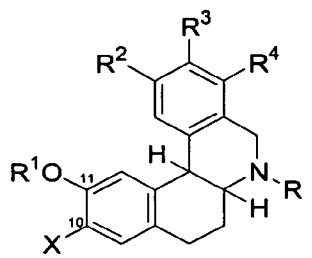
Clozapine-like agents include, but are not limited to the group consisting of olanzapine, clozapine, risperidone, sertindole, quetiapine, and ziprasidone. It appreciated that various combinations of the foregoing typical and atypical antipsychotic agents may be used in the methods and compositions described herein.

Any other antipsychotic agent, including any typical or atypical antipsychotic agent such as acetophenazine, acetophenazine maleate, triflupromazine, chlorprothixene, alentemol hydrobromide, alpertine, azaperone, batelapine maleate, benperidol, benzindopyrine hydrochloride, brofoxine, bromperidol, bromperidol decanoate, butaclamol hydrochloride, butaperazine, butaperazine maleate, carphenazine maleate, carvotroline hydrochloride, chlorpromazine hydrochloride, cinperene, cintriamide, clomacran phosphate, clopenthixol, clopimozide, clopipazan mesylate, chloroperone hydrochloride, clothiapine, clothixamide maleate, cyclophenazine hydrochloride, droperidol, etazolate hydrochloride, fenimide, flucindole, flumezapine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, fluspiperone, fluspirilene, flutroline, gevotroline hydrochloride, halopemide, haloperidol decanoate, iloperidone, imidoline hydrochloride, lenperone, mazapertine succinate, mesoridazine besylate, metiapine, milenperone, milipertine, molindone hydrochloride, naranol hydrochloride, neflumozide hydrochloride, ocaperidone, oxiperomide, penfluridol, pentiapine maleate, pinoxepin hydrochloride, pipamperone, piperacetazine, pipotiazine palmitate, piquindone hydrochloride, prochlorperazine edisylate, prochlorperazine maleate, promazine hydrochloride, remoxipride, remoxipride hydrochloride, rimcazole hydrochloride, seperidol hydrochloride, setoperone, spiperone, thioridazine hydrochloride, thiothixene hydrochloride, thioperidone hydrochloride, tiospirone hydrochloride, trifluoperazine hydrochloride, trifluperidol, triflupromazine hydrochloride, and ziprasidone hydrochloride, and the like, can also be used.

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is a known compound and is described in U.S. Pat. No. 5,229,382, incorporated herein by reference. Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, is described in U.S. Pat. No. 3,539,573 that is incorporated herein by reference. Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9 -tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one is described in U.S. Pat. No. 4,804,663, that is incorporated by

reference herein. Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Pat. Nos. 4,710,500, 5,112,838, and 5,238,945, incorporated by reference herein. Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl -1-piperazinyl)ethoxy]ethanol, is described in U.S. Pat. No. 4,879,288 that is incorporated by reference herein. Ziprasidone, 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihyd ro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in U.S. Pat. Nos. 4,831,031 and 5,312,925, incorporated by reference herein.

In one embodiment, the D_1 dopamine receptor agonist is a hexahydrobenzo[*a*]phenanthridine compound. Exemplary hexahydrobenzo[*a*]phenanthridine compounds for use in the method and composition described herein include, but are not limited to, compounds of having Formula **V**:



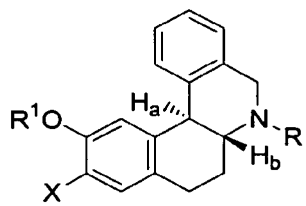
(**V**)

wherein R is hydrogen or C_1-C_4 alkyl; R^1 is hydrogen, acyl, such as C_1-C_4 alkanoyl, benzoyl, pivaloyl, and the like, or an optionally substituted phenyl protecting group; X is hydrogen, fluoro, chloro, bromo, iodo or a group of the formula -OR^5 wherein R^5 is hydrogen, C_1-C_4 alkyl, acyl, such as C_1-C_4 alkanoyl, benzoyl, pivaloyl, and the like; and R^2, R^3, and R^4 are each independently selected from hydrogen, C_1-C_4 alkyl, phenyl, fluoro, chloro, bromo, iodo, and a group -OR^6 wherein R^6 is hydrogen, acyl, such as C_1-C_4 alkanoyl, benzoyl, pivaloyl, and the like; and pharmaceutically acceptable salts thereof. It is appreciated that compounds having Formula **V** are chiral. It is understood that both *cis* enantiomers and both *trans* enantiomers of Formula **V** are contemplated as included herein.

As used herein, the term "acyl" refers to an optionally substituted alkyl or aryl radical connected through a carbonyl (C=O) group, such as optionally substituted alkanoyl, and optionally substituted aroyl or aryloyl. Illustrative acyl groups include, but are not limited to C_1-C_4 alkanoyl, acetyl, propionyl, butyryl, pivaloyl, valeryl, tolyl, trifluoroacetyl, anisyl, and the like.

In another embodiment, when X in Formula **V** is a group of the formula -OR^5 the groups R^1 and R^5 can be taken together to form a -CH_2- or -$(CH_2)_2$- group, thus representing a methylenedioxy or ethylenedioxy functional group bridging the C-10 and C-11 (see ring carbon numbering in Formula **V**) positions on the hexahydrobenzo[*a*]phenanthridine ring system.

In another embodiment, the D_1 dopamine receptor agonist for use in the method and composition described herein is represented by compounds having Formula **I**:



(I)

wherein H_a and H_b are *trans* across the ring fusion bond and wherein R, R_1, and X are as defined in Formula **V**, and pharmaceutically acceptable salts thereof. It is appreciated that compounds having Formula **I** are chiral. It is further appreciated that although a single enantiomer is depicted, both enantiomers are contemplated as included herein.

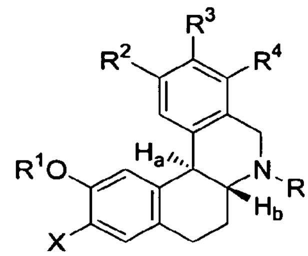
The term "C_1-C_4 alkyl" as used herein refers to straight-chain or branched alkyl groups comprising one to four carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, cyclopropylmethyl, and the like. The selectivity of the compounds for the dopamine D_1 and D_2 receptors may be affected by the nature of the nitrogen substituent. Optimal dopamine D_1 agonist activity has been noted where R in Formulae **I**, **II**, and **V** is hydrogen or methyl. One compound of Formula **I** for use in the method and composition of the present invention is *trans*-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride, denominated hereinafter as "dihydrexidine."

N-Alkylation may be used to prepare compounds of Formula **I**, **II**, and **V** wherein R is other than hydroge, and can be effected using a variety of known synthetic methods, including, but not limited to, reductive animation of the compounds wherein R = H with an aldehyde and a reducing agent, treatment of the same with an alkyl halide, treatment with a carboxylic acid in the presence of sodium borohydride, or treatment with carboxylic acid anhydrides followed by reduction, for example with lithium aluminum hydride or with borane as the reducing agent.

All active compounds described herein bear an oxygen atom at the C-11 position as shown in Formulae I, II and **V** above. The C-10 unsubstituted, C-11 hydroxy compounds possess dopamine D_1 antagonist, or weak agonist activity, depending on the alkyl group that is attached to the nitrogen atom. The more potent dopamine D_1 agonist compounds exemplified herein have a 10,11-dioxy substitution pattern, in particular, the 10,11-dihydroxy substituents. However, the 10,11-dioxy substituents need not be in the form of hydroxyl groups. Masked hydroxyl groups, or prodrug (hydroxyl protecting) groups can also be used. For example, esterification of the 10,11-hydroxyl groups with, for example, benzoic acid or pivalic acid ester forming compounds (*e.g.*, acid anhydrides) yields 10,11-dibenzoyl or dipivaloyl esters that are useful as prodrugs, *i.e.*, they will be hydrolyzed *in vivo* to produce the biologically active 10,11-dihydroxy compound. A variety of biologically acceptable carboxylic acids can also be used. Furthermore, the 10,11-dioxy ring substitution can be in the form of a 10,11-methylenedioxy or ethylenedioxy group. *In vivo*, body metabolism will cleave this linkage to provide the more active 10,11-dihydroxy functionality. Compound potency and receptor selectivity can also be affected by the nature of the nitrogen substituent.

In another embodiment of the method and composition described herein, C_2, C_3, and/or C_4-substituted *trans*-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridines can be used as the D_1 dopamine receptor agonist. The selectivity of these compounds for dopamine receptor subtypes varies, depending on the nature and positioning of substituent groups. Substitution at the C_2, C_3, and/or C_4 position on the benzophenanthridine ring system controls affinity for the dopamine receptor subtypes and concomitantly receptor selectivity. Thus, for example, 2-methyldihydrexidine has D_1 potency and efficacy comparable to dihydrexidine, while it has a five-fold enhanced selectivity for the D_1 receptor. In contrast, the compound 3-methyldihydrexidine, although retaining D_1 potency and efficacy comparable to dihydrexidine, has greater D_2 potency, making it less selective but better able to activate both types of receptors.

Exemplary of the C_2, C_3, and/or C_4-substituted trans-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridines for use as D_1 dopamine receptor agonists in the method and composition described herein include, but are not limited to compounds having Formula **II**:



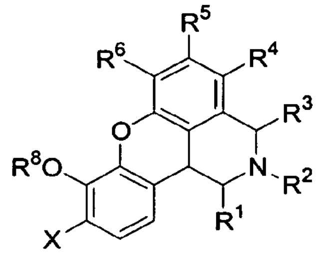
(II)

and pharmaceutically acceptable salts thereof, wherein H_a and H_b are *trans* across the ring fusion bond; R is hydrogen or C_1-C_4 alkyl; R^1 is hydrogen, acyl, such as C_1-C_4 alkanoyl, benzoyl, pivaloyl, and the like, or a phenoxy protecting group, such as a prodrug and the like; X is hydrogen, fluoro, chloro, bromo, or iodo, or a group of the formula $-OR^5$ wherein R^5 is hydrogen, C_1-C_4 alkyl, acyl, such as benzoyl, pivaloyl, and the like, or an optionally substituted phenoxy protecting group, provided that when X is a group of the formula $-OR^5$, the groups R^1 and R^5 can optionally be taken together to form a $-CH_2-$ or $-(CH_2)_2-$ group, thus representing a methylenedioxy or ethylenedioxy functional group bridging the C-10 and C-11 positions on the hexahydrobenzo[*a*]phenanthridine ring system (as labeled above in Formula **V**); and R^2, R^3, and R^4 are independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, phenyl, fluoro, chloro, bromo, iodo, or a group $-OR^6$ wherein R^6 is hydrogen, acyl, such as benzoyl, pivaloyl, and the like, or an optionally substituted phenyl protecting group. In another embodiment, at least one of R^2, R^3, and R^4 are other than hydrogen. It is appreciated that the phenoxy protecting groups used herein may diminish or block the reactivity of the nitrogen to which they are attached. In addition, the phenoxy protecting groups used herein may also serve as prodrugs, and the like. It is understood that the compounds of Formula **II** are chiral. It is further understood that although a single enantiomer is depicted, both enantiomers are contemplated as included in the invention described herein.

In accordance with the method and composition described herein, "C_1-C_4 alkoxy" as used herein refers to branched or straight chain alkyl groups comprising one to four carbon atoms bonded through an oxygen atom, including, but not limited to, methoxy, ethoxy, and t-butoxy. The compounds of Formula **II** are prepared using the same preparative chemical steps described for the preparation of the hexahydrobenzo[*a*]phenanthridine compounds (see Fig. 1) using the appropriately substituted benzoic acid acylating agent starting material instead of the benzoyl chloride reagent used in the initial reaction step. Thus, for example, the use of 4-

methylbenzoyl chloride will yield a 2-methyl-hexahydrobenzo[*a*]phenanthridine compound.

In another embodiment, chromeno[4,3,2-*de*]isoquinoline compounds can be used as the D_1 dopamine receptor agonist administered in combination therapy with a D_2 dopamine receptor antagonist. Exemplary compounds that are used in the method and composition described herein include, but are not limited to compounds having Formula **III**:



(III)

wherein R^1, R^2, and R^3 are each independently selected from hydrogen, C_1-C_4 alkyl, and C_2-C_4 alkenyl; R^8 is hydrogen, C_1-C_4 alkyl, acyl, or an optionally substituted phenoxy protecting group; X is hydrogen, halo including fluoro, chloro, bromo, and iodo, or a group of the formula -OR^9 wherein R^9 is hydrogen, C_1-C_4 alkyl, acyl, or an optionally substituted phenoxy protecting group, and R^4, R^5, and R^6 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, phenyl, halo, and a group -OR wherein R is hydrogen, acyl, such as benzoyl, pivaloyl, and the like, or an optionally substituted phenyl protecting group, and when X is a group of the formula -OR^9, the groups R^8 and R^9 can be taken together to form a group of the formula -CH_2- or -$(CH_2)_2$-. The compounds also comprise pharmaceutically acceptable salts thereof.

In this embodiment, "C_2-C_4 alkenyl" as used herein refers to branched or straight-chain alkenyl groups having two to four carbons, such as allyl, 2-butenyl, 3-butenyl, and vinyl.

In another embodiment, wherein compounds of Formula **III** are used in the method and composition described herein at least one of R_4, R_5, or R_6 is hydrogen. In another embodiment at least two of R_4, R_5, or R_6 are hydrogen.

One compound of Formula **III** for use in the method and composition described herein is (±)-8,9-dihydroxy-1,2,3,11b-tetrahydrochromeno[4,3,2-*de*]isoquinoline hydrobromide (**16a**), denominated hereinafter as "dinoxyline." Dinoxyline is synthesized from 2,3-dimethoxyphenol (**7**) and 4-bromoisoquinole (**10**),

as depicted in Fig. 2. The phenolic group is protected as the methoxymethyl ("MOM") derivative **8** followed by treatment with butyllithium, then with the substituted borolane illustrated, to afford the borolane derivative **9**.

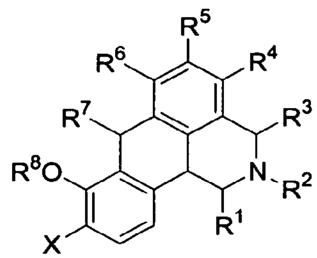
As shown in Fig. 2, this borolane derivative is then employed in a Pd-catalyzed Suzuki type cross coupling reaction with 5-nitro-4-bromoisoquinoline (**11**), prepared from bromoisoquinoline **10**. The resulting coupling product **12** is then treated with toluenesulfonic acid in methanol to remove the MOM protecting group of the phenol. Treatment of this nitrophenol **13** with potassium carbonate in DMF at 80 °C leads to ring closure with loss of the nitro group, affording the basic tetracyclic chromenoisoquinoline nucleus **14**. Catalytic hydrogenation effects reduction of the nitrogen-containing ring to yield **15a**. Use of boron tribromide to cleave the methyl ether linkages gives the parent compound **16a**.

It is apparent that by appropriate substitution on the isoquinoline ring a wide variety of substituted compounds can be obtained. Substitution onto the nitrogen atom in either **14** or **15a**, followed by reduction will readily afford a series of compounds substituted with lower alkyl groups on the nitrogen atom. Likewise, the use of alkyl substituents on the 1, 3, 6, 7, or 8 positions of the nitroisoquinoline **11** leads to a variety of ring-substituted compounds. In addition, the 3-position of **14** can also be directly substituted with a variety of alkyl groups. Similarly, replacement of the 4-methoxy group of **9**, in Fig. 2, with fluoro, chloro, or alkyl groups leads to the subject compounds with variations at X_9. When groups are present on the nucleus that are not stable to the catalytic hydrogenation conditions used to convert **14** to **15a**, reduction can be accomplished using sodium cyanoborohydride at slightly acidic pH. Further, formation of the N-alkyl quaternary salts of derivatives of **14** gives compounds that are also easily reduced with sodium borohydride, leading to derivatives of **15a**.

Fig. 2 also illustrates the synthesis of *N*-substituted chromenoisoquinolines **15** and **16**. Compound **15a** is *N*-alkylated under standard conditions to provide substituted derivatives. Alkylating agents, such as R-L, where R is methyl, ethyl, propyl, allyl, and the like, and L is a suitable leaving group such as halogen, methylsulfate, or a sulfonic acid derivative, are used to provide the corresponding *N*-alkyl derivatives. The aromatic methyl ethers of compounds 15 are then removed under standard conditions, such as upon treatment with BBr_3 and the

like. It appreciated that N-alkylation may be followed by other chemical transformations to provide the substituted derivatives described herein. For example, alkylation with an allyl halide followed by hydrogenation of the allyl double bond provides the corresponding *N*-propyl derivative.

In another embodiment, tetrahydronaphtho[1,2,3-*de*]isoquinoline compounds are used as the D_1 dopamine receptor agonist for co-administration with a D_2 dopamine receptor antagonist. Exemplary compounds for use in the method and composition described herein include, but are not limited to compounds having Formula IV:



(IV)

and pharmaceutically acceptable salts thereof, wherein R^1, R^2, and R^3 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, and C_2-C_4 alkenyl; R^4, R^5, and R^6 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, phenyl, halogen, and a group having the formula -OR, where R is hydrogen, acyl, such as benzoyl, pivaloyl, and the like, or an optionally substituted phenyl protecting group; R^7 is selected from the group consisting of hydrogen, hydroxy, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkoxy, and C_1-C_4 alkylthio; R^8 is hydrogen, C_1-C_4 alkyl, acyl, or an optionally substituted phenyl protecting group; and X is hydrogen, fluoro, chloro, bromo, or iodo.

In another embodiment of Formula **IV**, X is a group having the formula $-OR^9$, where R^9 is hydrogen, C_1-C_4 alkyl, acyl, or an optionally substituted phenyl protecting group; or the groups R^8 and R^9 are taken together to form a divalent group having the formula $-CH_2-$ or $-(CH_2)_2-$.

In accordance with the method and composition described herein, the term "pharmaceutically acceptable salts" as used herein refers to those salts formed using organic or inorganic acids that are suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like. Acids suitable for forming pharmaceutically acceptable salts of biologically active compounds having amine functionality are well known in the art. The salts can

be prepared according to conventional methods *in situ* during the final isolation and purification of the present compounds, or separately by reacting the isolated compounds in free base form with a suitable salt forming acid.

In accordance with the method and composition described herein, the term "phenoxy protecting group" as used herein refers to substituents on the phenolic oxygen which prevent undesired reactions and degradations during synthesis and which can be removed later without effect on other functional groups on the molecule. Such protecting groups and the methods for their application and removal are well known in the art. They include ethers, such as methyl, isopropyl, t-butyl, cyclopropylmethyl, cyclohexyl, allyl ethers and the like; alkoxyalkyl ethers such as methoxymethyl or methoxyethoxymethyl ethers and the like; alkylthioalkyl ethers such a methylthiomethyl ethers; tetrahydropyranyl ethers; arylalkyl ethers such as benzyl, o-nitrobenzyl, p-methoxybenzyl, 9-anthrylmethyl, 4-picolyl ethers and the like; trialkylsilyl ethers such as trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl ethers and the like; alkyl and aryl esters such as acetates, propionates, n-butyrates, isobutyrates, trimethylacetates, benzoates and the like; carbonates such as methyl, ethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, vinyl, benzyl and the like; and carbamates such as methyl, isobutyl, phenyl, benzyl, dimethyl and the like.

One compound for use in accordance with the method and composition described herein as a D_1 dopamine receptor agonist for co-administration with a D_2 dopamine receptor antagonist is (±)-8,9-dihydroxy-2,3,7,11b-tetrahydro-1*H*-naphtho-[1,2,3-*de*]-isoquinoline (**29**) denominated hereinafter as "dinapsoline." Dinapsoline is synthesized from 2-methyl-2,3-dihydro-4(1*H*)-isoquinolone (**20**) according to the procedure depicted generally in Figs. 3 and 4. Side chain bromination of ethyl 2-toluate (**17**) with NBS in the presence of benzoyl peroxide produced compound **18**. Alkylation of sarcosine ethyl ester with compound **18** afforded compound **19**, which after Dieckmann condensation and subsequent decarboxylation on acidic hydrolysis yielded compound **20**.

As shown in Fig. 4, *ortho*-directed lithiation of 2,3-dimethoxy-*N,N'*-diethylbenzamide (**21**) with *sec*-butyllithium/TMEDA in ether at -78 °C and condensation of the lithiated species with compound **20** followed by treatment with *p*-toluene sulfonic acid at reflux gave spirolactone **22** in modest yield.

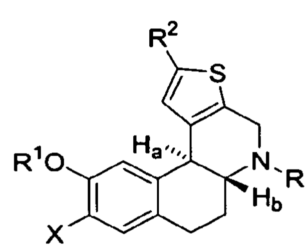
N-Demethylation of **22** with 1-chloroethylchloroformate followed by methanolysis of the intermediate afforded compound **23**, that on treatment with *p*-toluenesulfonyl chloride and triethylamine provided compound **24**.

Early attempts to synthesize compound **24** directly by condensation of 2-*p*-toluenesulfonyl-2,3-dihydro-4(1*H*)-isoquinolone with lithiated compound **21** in THF or ether, followed by lactonization with acid provided only trace amounts (< 5%) of compound **24**. Enolization of 2-*p*-toluenesulfonyl-2,3-dihydro-4(1*H*)-isoquinolone under the basic reaction conditions is one possible explanation for the poor yield.

Hydrogenolysis of compound **24** in glacial acetic acid in the presence of 10% palladium on carbon gave compound **25** that on reduction with diborane afforded intermediate compound **26**. Cyclization of compound **26** with concentrated sulfuric acid at low temperature provided compound **22**. *N*-Detosylation of compound **22** with Na/Hg in methanol buffered with disodium hydrogen phosphate gave compound **28**. Finally, compound **28** was treated with boron tribromide to effect methyl ether cleavage yielding dinapsoline (**29**) as its hydrobromide salt.

Alternatively, dinapsoline and compounds related to dinapsoline may also be synthesized according to the procedure described by Sattelkau, Qandil, and Nichols, "An efficient synthesis of the potent dopamine D_1 agonst dinapsoline by construction and selective reduction of 2'-azadimethoxybenzanthrone," *Synthesis* 2:262-66 (2001), the entirety of the description of which is incorporated herein by reference.

In another embodiment, heterocyclic-fused phenanthridine compounds, such as thieno[1,2-*a*]phenanthridines, and the like, are used as the D_1 dopamine receptor agonist for administration in combination therapy with a D_2 dopamine receptor antagonist to patients with neurological disorders. Exemplary compounds for use in the methods and compositions described herein include, but are not limited to, compounds having Formula **VI**:

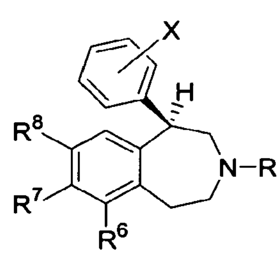


(VI)

and pharmaceutically acceptable salts thereof, wherein H*a* and H*b* are *trans* across the ring fusion bond; R is hydrogen or C_1-C_4 alkyl; R^1 is hydrogen, acyl, such as C_1-C_4 alkanoyl, benzoyl, pivaloyl, and the like, or a phenoxy protecting group; X is hydrogen, fluoro, chloro, bromo, iodo, or a group of the formula -OR^3 wherein R^3 is hydrogen, alkyl, acyl, or a phenoxy protecting group, provided that when X is a group of the formula-OR^3, the groups R^1 and R^3 can be taken together to form a -CH_2- group or a -$(CH_2)_2$- group, thus representing a methylenedioxy or ethylenedioxy functional group bridging the C-10 and C-11 positions on the hexahydrobenzo[*a*]phenanthridine ring system (as labeled above in Formula **V**); and R^2 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, phenyl, fluoro, chloro, bromo, iodo, or a group -OR^4 wherein R^4 is hydrogen, alkyl, acyl, or a phenoxy protecting group. It is appreciated that the compounds having Formula **VI** are chiral. It is further appreciated that though a single enantiomer is depicted, both enantiomers are contemplated as included herein.

Exemplary compounds of Formula **VI** include, but are not limited to, ABT 431 (X = CH_3CO_2, R^1 = CH_3CO, R^2 = $CH_3(CH_2)_2$, R = H) and A 86929 (X = OH, R^1 = H, R^2 = $CH_3(CH_2)_2$, R = H).

In another embodiment, phenyltetrahydrobenzazepine compounds can be used as the D_1 dopamine receptor agonist for co-administration with a D_2 dopamine receptor antagonist. Exemplary compounds for use in the method and composition described herein include, but are not limited to compounds having Formula **VII**:



(VII)

wherein R is hydrogen, alkyl, alkenyl, optionally substituted benzyl, or optionally substituted benzoyl; R^6, R^7, and R^8 are each independently selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, and acyloxy; and X is hydrogen, halogen, hydroxy, alkyl, alkoxy, or acyloxy. Illustrative compounds having the Formula **VII** include SKF 38393 (R^6 = H, R^7 = R^8 = OH, R = H, X = H), SKF 82958 (R^6 = Cl, R^7 = R^8 =

OH, R = $CH_2CH{=}CH_2$, X = H), SKF 81297 (R^6 = Cl, R^7 = R^8 = OH, R = H, X = H), and SCH 23390 (R^6 = H, R^7 = Cl, R^8 = OH, R = CH_3, X = H).

The D_1 dopamine receptor agonists, for co-administration with the D_2 dopamine receptor antagonists, vary in their selectivity for dopamine D_1 and D_2 receptor subtypes. In some embodiments, these dopamine receptor agonists exhibit activity at both the D_1 and D_2 dopamine receptor subtypes. In one embodiment, this activity at the D_1 and D_2 dopamine receptor subtypes can be about equal. In another embodiment, this activity at the D_1 and D_2 dopamine receptor subtypes can be characterized by being selective for these two dopamine receptor subtypes as compared to other dopamine receptor subtypes. In this latter embodiment, the activity exhibited by the dopamine receptor agonists at the D_1 and D_2 dopamine receptor subtypes may be about equal or not. Among exemplary compounds, dihydrexidine is 10-fold D_1:D_2 selective and dinapsoline is 5-fold D_1:D_2 selective while dinoxyline has equally high affinity for both receptor subtypes.

The compounds for use in the method and composition described herein can be formulated in conventional drug dosage forms, and can be in the same or different compositions. In accordance with the composition and method described herein "co-administration" means administration in the same or different compositions or in the same or different dosage forms or by the same or different routes of administration in any manner which provides effective levels of the active ingredients in the body at the same time. Combinations of D_1 dopamine receptor agonists and D_2 dopamine receptor antagonists can also be used in the "co-administration" protocols described above.

"Effective amounts" are amounts of the compounds which prevent, reduce, or stabilize one or more of the clinical symptoms of disease in a patient suffering from the neurological disorder whether such improved patient condition is permanent or temporary.

In one embodiment, the drug dosage forms are formulated for oral ingestion by the use of such dosage forms as syrups, sprays, or other liquid dosage forms, a gel-seal, or a capsule or caplet. Syrups for either use may be flavored or unflavored and may be formulated using a buffered aqueous solution of the active ingredients as a base with added caloric or non-caloric sweeteners, flavor oils and pharmaceutically acceptable surfactant/dispersants. Other liquid dosage forms,

including liquid solutions or sprays can be prepared in a similar manner and can be administered buccally, sublingually, or by oral ingestion.

In one embodiment, buccal and sublingual administration is used and comprises contacting the oral and pharyngeal mucosa of the patient with the D_1 agonist and the D_2 antagonist either in a pharmaceutically acceptable liquid dosage form, such as a syrup or a spray, or in a saliva-soluble dosage form which is held in the patient's mouth to form a saliva solution. Exemplary of saliva-soluble dosage forms are lozenges, tablets, and the like.

In one embodiment, lozenges can be prepared, for example, by art-recognized techniques for forming compressed tablets where the active ingredients are dispersed on a compressible solid carrier, optionally combined with any appropriate tableting aids such as a lubricant (*e.g.*, magnesium-stearate) and are compressed into tablets. The solid carrier component for such tableting formulations can be a saliva-soluble solid, such as a cold water-soluble starch or a monosaccharide or disaccharide, so that the lozenge will readily dissolve in the mouth to release the active ingredients. The pH of the above-described formulations can range from about 4 to about 8.5. Lozenges can also be prepared utilizing other art-recognized solid unitary dosage formulation techniques.

In another embodiment, tablets are used. Tablets can be prepared in a manner similar to that described for preparation of lozenges or by other art-recognized techniques for forming compressed tablets such as chewable vitamins. Tablets can be prepared by direct compression, by wet granulation, or by dry granulation, and usually incorporate diluents, binders, lubricants and disintegrators as well as the active ingredients. Typical diluents include, for example, starches, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride, powdered sugar, microcrystalline cellulose, carboxymethyl cellulose, and powdered cellulose derivatives.

Typical binders include starches, gelatin and sugars such as lactose, fructose, glucose and the like, natural and synthetic gums, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like, polyethylene glycol, ethylcellulose, and waxes. Typical lubricants include talc, magnesium and calcium stearate, stearic acid, and hydrogenated vegetable oils. Typical tablet disintegrators include starches, clays, celluloses, algins and gums, corn and potato starches,

methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp, carboxymethylcellulose, and sodium lauryl sulfate. Tablets can be coated with sugar as a flavor and sealant, or tablets can be formulated as chewable tablets, by using substances such as mannitol in the formulation, according to formulation methods known in the art, or as instantly dissolving tablet-like formulations according to known methods.

Solid dosage forms for oral ingestion administration also include such dosage forms as caplets, capsules, and gel-seals. Such solid dosage forms can be prepared using standard tableting protocols and excipients to provide capsules, caplets, or gel-seals containing the active ingredients. The usual diluents for capsules and caplets include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders. Any of the solid dosage forms for use in accordance with the invention, including lozenges and tablets, may be in a form adapted for sustained release of the active ingredients.

In another embodiment, parenteral administration is used. Parenteral administration can be accomplished by injection of a liquid dosage form, such as by injection of a solution of the D_1 agonist and the D_2 antagonist dissolved in a pharmaceutically acceptable buffer. Such parenteral administration can be intradermal, subcutaneous, intramuscular, intraperitoneal, or intravenous. Transdermal patches known in the art can also be used.

In accordance with one embodiment, a pharmaceutical composition is provided comprising effective amounts of the active ingredients, and a pharmaceutically acceptable carrier therefor. A "pharmaceutically acceptable carrier" for use in accordance with the method and composition described herein is compatible with other reagents in the pharmaceutical composition and is not deleterious to the patient. The pharmaceutically acceptable carrier formulations for pharmaceutical compositions adapted for oral ingestion or buccal/sublingual administration including lozenges, tablets, capsules, caplets, gel-seals, and liquid dosage forms, including syrups, sprays, and other liquid dosage forms, have been described above.

The active ingredients can also be adapted for parenteral administration in accordance with this invention using a pharmaceutically acceptable carrier adapted for use in a liquid dose form. Thus, the active ingredients can be

administered dissolved in a buffered aqueous solution typically containing a stabilizing amount (1-5% by weight) of albumin or blood serum. Such a liquid solution can be in the form of a clarified solution or a suspension. Exemplary of a buffered solution administered parenterally in accordance with this invention is phosphate buffered saline prepared as follows:

A concentrated (20x) solution of phosphate buffered saline (PBS) is prepared by dissolving the following reagents in sufficient water to make 1,000 mL of solution: sodium chloride, 160 grams; potassium chloride, 4.0 grams; sodium hydrogen phosphate, 23 grams; potassium dihydrogen phosphate, 4.0 grams; and optionally phenol red powder, 0.4 grams. The solution is sterilized by autoclaving at 15 pounds of pressure for 15 minutes and is then diluted with additional water to a single strength concentration prior to use.

In another embodiment, aerosol administration of the active ingredients can be used. Aerosol and dry powder formulations for delivery to the lungs and devices for delivering such formulations to the endobronchial space of the airways of a patient are described in U.S. Patent No. 6,387,886, incorporated herein by reference, and in Zeng et al., *Int'l J. Pharm.*, vol. 191: 131-140 and Odumu et al., *Pharm. Res.*, vol. 19: 1009-1012, although any other art-recognized formulations or delivery devices can be used. The D_1 dopamine receptor agonist and the D_2 dopamine receptor antagonist can be in the form of an aerosol or a dry powder diluted in, for example, water or saline, the diluted solution having a pH of, for example, between about 5.5 and about 7.0.

In one embodiment the solution can be delivered using a nebulized aerosol formulation, nebulized by a jet, ultrasonic or electronic nebulizer, capable of producing an aerosol with a particle size of between about 1 and about 5 microns, for example. In another embodiment the formulation can be administered in dry powder form where the active ingredient comprises part or all of the mass of the powder delivered. In this embodiment, the formulation can be delivered using a dry powder or metered dose inhaler, or the like. The powder can have average diameters ranging from about 1 to about 5 microns formed by media milling, jet milling, spray drying, or particle precipitation techniques.

The doses of the D_1 agonist and the D_2 antagonist for use in the method and composition depend on many factors, including the indication being treated and

the overall condition of the patient. For example, in one embodiment effective amounts of the present compounds range from about 1.0 ng/kg to about 15 mg/kg of body weight. In another embodiment effective amounts range from about 50 ng/kg to about 10 mg/kg of body weight. In another embodiment effective amounts range from about 200 ng/kg to about 5 mg/kg of body weight. In another embodiment effective amounts range from about 300 ng/kg to about 3 mg/kg of body weight. In another embodiment effective amounts range from about 500 ng/kg to about 1 mg/kg of body weight. In another embodiment effective amounts range from about 1 μg/kg to about 0.5 mg/kg of body weight. In general, treatment regimens utilizing compounds in accordance with the present invention comprise administration of from about 10 ng to about 1 gram of the compounds for use in the method and composition described herein per day in multiple doses or in a single dose. Effective amounts of the compounds can be administered using any regimen such as twice daily, for at least one day to about twenty-one days.

The following examples are illustrative of the compounds for use in the presently claimed methods and compositions and are not intended to limit the invention to the disclosed compounds. Other compounds that can be used in accordance with the claimed method include those compounds described in U.S. Patent Nos. 5,047,536, 5,420,134, 5,959,110, 6,413,977, and 6,147,072. Each of these patents is hereby incorporated by reference. Variations and modifications of the exemplified compounds obvious to one skilled in the art are also intended to be within the scope of the invention as specified in the claims.

EXAMPLES

With reference to the experimental procedures described herein, unless otherwise indicated, the following procedures were used where applicable. Solvent removal was accomplished by rotary evaporation under reduced pressure. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian VXR 500S (500 MHz) NMR instrument and chemical shifts were reported in values (ppm) relative to TMS. The IR spectra were recorded as KBr pellets or as a liquid film with a Perkin Elmer 1600 series FTIR spectrometer. Chemical ionization mass spectra (CIMS) were recorded on a Finnigan 4000 quadruple mass spectrometer. High resolution CI

spectra were recorded using a Kratos MS50 spectrometer. Elemental analysis data were obtained from the microanalytical laboratory of Purdue University, West Lafayette, IN. THF was distilled from benzophenone-sodium ketyl under N_2 immediately before use. 1,2-Dichloroethane was distilled from phosphorous pentoxide before use.

EXAMPLE 1

2-(N-benzyl-N-benzoyl)-6,7-dimethoxy-3,4-dihydro-2-napthylamine (**2a**). To a solution of 4.50 g (21.8 mmol) of 6,7-dimethoxy-β-tetralone (**1**) in 100 mL of toluene was added 2.46 g (23 mmol) of benzylamine. The reaction was heated at reflux overnight under N_2 with continuous water removal. The reaction was cooled, and the solvent was removed to yield N-benzyl enamine as a brown oil.

This residue was dissolved in 80 mL of CH_2Cl_2, and to this was added 2.43 g (24 mmol) of triethylamine, and the solution was cooled in an ice bath. Benzoyl chloride (3.37 g, 24 mmol) was then dissolved in 15 mL of CH_2Cl_2 and this solution was then added dropwise to the cold stirring N-benzyl enamine solution. After complete addition the reaction was allowed to warm to room temperature and was left to stir overnight. The mixture was then washed successively with 2 X 50 mL of 5% aqueous HCl, 2 X 50 mL of 1 N NaOH, saturated NaCl solution, and was then dried over $MgSO_4$. After filtration, the filtrate was concentrated. Crystallization from diethyl ether gave 5.6 g (64%) of enamide **2**: mp 109-110 °C; IR (KBr) 1620 cm^{-1}; CIMS (isobutane, M + 1) 400; ^{1}H-NMR ($CDCl_3$) δ 7.64 (m, 2, ArH), 7.33 (m, 8, ArH), 6.52 (s, 1, ArH), 6.38 (s, 1, ArH), 6.05 (s, 1, ArCH), 4.98 (s, 2, $ArCH_2$ N), 3.80 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 2.47 (t, 2, CH_2, J = 8.1 Hz), 2.11 (t, 2, CH_2, J = 8.1 Hz).

Trans-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine-5-one (**3a**). A solution of 3.14 g (7.85 mmol) of the 6,7-dimethoxyenamide **2**, in 300 mL of THF, was introduced into an Ace Glass 250 mL photochemical reactor. This solution was stirred while irradiating for 5 hours with a 450 watt Hanovia medium pressure, quartz, mercury-vapor lamp seated in a water cooled, quartz immersion well. The solution was concentrated and crystallized from ether to provide 1.345 g (42.9%) of **3a**: mp 183-186 °C; IR (KBr) 1655, 1640 cm^{-1}; CIMS (isobutane, M + 1) 400; ^{1}H-NMR ($CDCl_3$) δ 8.19 (m, 1 ArH), 7.52 (m, 1,

ArH), 7.46 (m, 2, ArH), 7.26 (m, 5, ArH), 6.92 (s, 1, ArH), 6.63 (s, 1, ArH), 5.35 (d, 1, $ArCH_2N$, J = 16.0 Hz), 4.78 (d, 1, $ArCH_2$ N, J = 16.0 Hz), 4.37 (d, 1, Ar_2CH, J = 11.3 Hz), 3.89 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 3.80 (m, 1 CHN), 2.67 (m, 2, $ArCH_2$), 2.25 (m, 1, CH_2CN), 1.75 (m, 1, CH_2CN).

Trans-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (**4a**). A solution of 1.20 g (3 mmol) of **3a**, in 100 mL of dry THF was cooled in an ice-salt bath and 6.0 mL of 1 M BH_3 was added via syringe. The reaction was heated at reflux overnight. Water (10 mL) was added dropwise, and the reaction mixture was concentrated by distillation at atmospheric pressure. The residue was stirred with 50 mL of toluene, 1.0 mL of methane sulfonic acid was added, and the mixture was heated with stirring on the steam bath for one hour. The mixture was diluted with 40 mL of water and the aqueous layer was separated. The toluene was extracted several times with water, and the aqueous layers were combined. After basification of the aqueous phase with conc. ammonium hydroxide, the free base was extracted into 5 X 25 mL of CH_2Cl_2. This organic extract was washed with saturated NaCl solution, and dried over $MgSO_4$. After filtration, the organic solution was concentrated, the residue was taken up into ethanol, and carefully acidified with concentrated HCl. After drying several times by azeotropic distillation of ethanol, crystallization from ethanol afforded 0.97 g (76.5%) of the salt **4a**: mp 235-237 °C; CIMS (NH_3, M + 1) 386; ^{1}H-NMR ($CDCl_3$, free base) δ 7.37 (m, 9 ArH), 6.89 (s, 1, ArH), 6.74 (s, 1, ArH), 4.07 (d, 1, Ar_2CH, J = 10.7 (Hz), 3.90 (s, 3, OCH_3), 3.82 (m, 2, $ArCH_2N$), 3.79 (s, 3, OCH_3), 3.52 (d, 1 $ArCH_2N$, J = 15.3 Hz), 3.30 (d, 1, $ArCH_2$), J = 13.1 Hz), 2.86 (m, 2, CHN, $ArCH_2$), 2.30 (m, 2, $ArCH_2$, CH_2CN), 1.95 (m, 1, CH_2CN).

Trans-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (**5a**). A solution of 0.201 g (0.48 mmol) of the 6-benzyl hydrochloride salt **4a** in 50 mL of 95% ethanol containing 50 mg of 10% Pd-C catalyst was shaken at room temperature under 50 psig of H_2 for 8 hours. After removal of the catalyst by filtration, the solution was concentrated to dryness and the residue was recrystallized from acetonitrile to afford 0.119 g (75%) of **5a** as a crystalline salt: mp 243-244 °C; CIMS (NH_3, M + 1) 296; ^{1}H-NMR ($CDCl_3$, free base) δ 7.46 (d, 1, ArH, J = 6.1 Hz), 7.24 (m, 3, ArH), 6.91 (s, 1, ArH), 6.74 (s, 1,

ArH), 4.09 (s, 2, $ArCH_2N$), 3.88 (s, 3, OCH_3), 3.78 (m, 4, OCH_3, Ar_2CH), 2.87 (m, 3, CHN, $ArCH_2$), 2.17 (m, 1, CH_2CN), 1.61 (m, 2, NH, CH_2CN).

Trans-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (dihydrexidine, **6a**). A suspension of 0.109 g (0.33 mmol) of the 10,11-dimethoxy salt **5a**, in 1.5 mL of 48% HBr, was heated at reflux, under N_2, for 3 hours. The reaction mixture was concentrated to dryness under high vacuum. This material was dissolved in water and neutralized to the free base with $NaHCO_3$, while cooling the solution in an ice bath. The free base was extracted into chloroform, dried, filtered, and concentrated in vacuo. The residue was dissolved in ethanol and carefully neutralized with conc. HCl. After removal of the volatiles, the salt was crystallized as a solvate from methanol. This afforded 30 mg (25.2%) of **6**, solvated with a stoichiometry of 1 molecule of amine salt and 1.8 molecules of CH_3OH, as pale yellow crystals: mp 195 °C; CIMS (isobutane, M + 1) 268; ^{1}H-NMR (DMSO, HBr salt) δ 9.40 (bs, 1, $^+NH_2$), 9.22 (bs, 1, $^+NH_2$), 8.76 (bs, 2, OH), 7.38 (m, 4, ArH), 6.72 (s, 1, ArH), 6.63 (s, 1, ArH), 4.40 (s, 2, $ArCH_2N^+$), 4.16 (d, 1, Ar_2CH, J = 11.1 Hz), 3.00 (m, 1, CHN^+), 2.75 (m, 2, $ArCH_2$), 2.17 (m, 1, CH_2CN^+), 1.90 (m, 1, CH_2CN^+).

EXAMPLE 2

2-(N-benzyl-N-4-methylbenzoyl)-6,7-dimethoxy-3,4-dihydro-2-naphthylamine (**2b**). To a solution of 4.015 g (19.5 mmol) of 6,7-dimethoxy-β-tetralone in 100 mL of toluene was added 2.139 g (1.025 equiv.) of benzylamine. The reaction was heated at reflux overnight under N_2 with continuous water removal. The reaction was cooled and the solvent was removed to yield N-benzyl enamine as a brown oil.

The 4-methylbenzoyl chloride acylating agent was prepared by suspending 3.314 g (24.3 mmol) of 4-toluic acid in 200 mL benzene. To this solution was added 2.0 equivalents (4.25 mL) of oxalyl chloride, dropwise via a pressure-equalizing dropping funnel at O °C. Catalytic DMF (2-3 drops) was added to the reaction mixture and the ice bath was removed. The progress of the reaction was monitored using infrared spectroscopy. The solvent was removed and the residual oil was held under high vacuum overnight.

The resulting N-benzyl enamine residue was dissolved in 100 mL of CH_2Cl_2, and to this solution was added 2.02 g (19.96 mmol) of triethylamine at O °C. The 4-methylbenzoyl chloride (3.087 g, 19.96 mmol) was dissolved in 20 mL CH_2Cl_2 and this solution was added dropwise to the cold, stirring N-benzyl enamine solution. The reaction was allowed to warm to room temperature and was left to stir under N_2 overnight. The reaction mixture was washed successively with 2 X 30 mL of 5% aqueous HCl, 2 X 30 mL of saturated sodium bicarbonate solution, saturated NaCl solution, and was dried over $MgSO_4$. After filtration, the filtrate was concentrated. Crystallization from diethyl ether gave 5.575 g (69.3%) of the enamide **2b**: mp 96-98 °C; CIMS (isobutane, M + 1) 414; ^{1}H-NMR ($CDCl_3$) δ 7.59 (d, 2, ArH), 7.46 (m, 3, ArH), 7.35 (m, 3, ArH), 7.20 (d, 2, ArH), 6.60 (s, 1, ArH), 6.45 (s, 1, ArH), 6.18 (s, 1, ArCH), 5.01 (s, 2, $ArCH_2N$), 3.80 (S, 3, OCH_3), 3.78 (s, 3, OCH_3), 2.53 (t, 2, $ArCH_2$), 2.37 (s, 3, $ArCH_3$), 2.16 (t, 2, CH_2).

<u>Trans-2-methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine-5-one (**3b**).</u> A solution of 4.80 g (11.62 mmol) of the 6,7-dimethoxyenamide **2b**, in 500 mL of THF, was introduced to an Ace Glass 500 mL photochemical reactor. This solution was stirred while irradiating for 2 hours with a 450 watt Hanovia medium pressure, quartz, mercury-vapor lamp seated in a water cooled, quartz immersion well. The solution was concentrated and crystallized from diethyl ether to provide 2.433 (50.7%) of the 10,11-dimethoxy lactam **3b**: mp 183-195 °C; CIMS (isobutane, M + 1) 414; ^{1}H-NMR ($CDCl_3$) δ 8.13 (d, 1, ArH), 7.30 (s, 1, ArH), 7.23 (m, 6, ArH), 6.93 (s, 1, ArH), 6.63 (s, 1, ArH), 5.38 (d, 1, $ArCH_2N$), 5.30 (d, 1, $ArCH_2N$), 4.34 (d, 1, Ar_2CH, J = 11.4 Hz), 3.89 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 3.76 (m, 1, CHN), 2.68 (m, 2, $ArCH_2$), 2.37 (s, 3, $ArCH_3$), 2.25 (m, 1, CH_2CN), 1.75 (m, 1, CH_2CN).

<u>Trans-2-methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (**4b**).</u> A solution of 1.349 g (3.27 mmol) of the lactam **3b**, in 100 mL dry THF was cooled in an ice-salt bath and 4.0 equivalents (13.0 mL) of 1.0 molar BH_3 was added through a syringe. The reaction was heated at reflux under nitrogen overnight. Methanol (10 mL) was added dropwise to the reaction mixture and reflux was continued for 1 hour. The solvent was removed. The residue was chased two times with methanol and twice with ethanol. The residue was placed under high vacuum (0.05 mm Hg) overnight. The

residue was dissolved in ethanol and was carefully acidified with concentrated HCl. The volatiles were removed and the product was crystallized from ethanol to afford 1.123 g (78.9%) of the hydrochloride salt **4b**: mp 220-223 °C; CIMS (isobutane, M + 1) 400; ^{1}H-NMR ($CDCl_3$, free base) δ 7.37 (d, 2, ArH), 7.33 (m, 2, ArH), 7.26 (m, 1, ArH), 7.22 (s, 1, ArH), 7.02 (d, 1, ArH), 6.98 (d, 1, ArH), 6.89 (s, 1, ArH), 6.72 (s, 1, ArH), 4.02 (d, 1, Ar_2CH, J = 10.81 Hz), 3.88 (s, 3, OCH_3), 3.86 (d, 1, $ArCH_2N$), 3.82 (m, 1, $ArCH_2N$), 3.78 (s, 3, OCH_3), 3.50 (d, 1, $ArCH_2N$), 3.30 (d, 1, $ArCH_2N$), 2.87 (m, 1, $ArCH_2$), 2.82 (m, 1, CHN), 2.34 (m, 1, CH_2CN), 2.32 (s, 3, $ArCH_3$), 2.20 (m, 1, $ArCH_2$), 1.93 (m, 1, CH_2CN).

Trans-2-methyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (**5b**). A solution of 0.760 g (1.75 mmol) of the 6-benzyl derivative **4b** in 100 mL of 95% ethanol containing 150 mg of 10% Pd/C catalyst was shaken at room temperature under 50 psig of H_2 for 8 hours. After removal of the catalyst by filtration through Celite, the solution was concentrated to dryness and the residue was recrystallized from acetonitrile to afford 0.520 g (86.2%) of **5b** as a crystalline salt: mp 238-239 °C; CIMS (isobutane, M + 1) 310; ^{1}H-NMR (DMSO, HCl salt) δ 10.04 (s, 1, NH), 7.29 (d, 1, ArH), 7.16 (m, 2, ArH), 6.88 (s, 1, ArH), 6.84 (s, 1, ArH), 4.31 (s, 2, $ArCH_2N$), 4.23 (d, 1, Ar_2CH, J = 10.8 Hz), 3.76 (s, 3, OCH_3), 3.70 (s, 3, OCH_3), 2.91 (m, 2, $ArCH_2$), 2.80 (m, 1, CHN), 2.49 (s, 3, $ArCH_3$), 2.30 (m, 1, CH_2CN), 2.09 (m, 1, CH_2CN).

Trans-2-methyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (**6b**). The 10,11-dimethoxy hydrochloride salt **5b** (0.394 g, 1.140 mmol) was converted to its free base. The free base was dissolved in 35 mL of CH_2Cl_2 and the solution was cooled to -78 °C. A 1.0 molar solution of BBr_3 (4.0 eq., 4.56 mL) was added slowly through a syringe. The reaction was stirred under N_2 overnight with concomitant warming to room temperature. Methanol (7.0 mL) was added to the reaction mixture and the solvent was removed. The residue was placed under high vacuum (0.05 mm Hg) overnight. The residue was dissolved in water and was carefully neutralized to its free base initially with sodium bicarbonate and finally with ammonium hydroxide (1-2 drops). The free base was isolated by suction filtration and was washed with cold water. The filtrate was extracted several times with dichloromethane and the organic extracts were dried, filtered, and concentrated. The filter cake and the organic residue were

combined, dissolved in ethanol, and carefully acidified with concentrated HCl. After removal of the volatiles, the HCl salt was crystallized as a solvate from methanol in a yield of 0.185 g (51%) of **6b**: mp 190 °C (dec.); CIMS (isobutane, M + 1) 282; ^{1}H-NMR (DMSO, HCl salt) δ 9.52 (s, 1, NH), 8.87 (d, 2, OH), 7.27 (d, 1, ArH), 7.20 (s, 1, ArH), 7.15 (d, 1, ArH), 6.72 (s, 1, ArH), 6.60 (s, 1, ArH), 4.32 (s, 2, $ArCH_2N$), 4.10 (d, 1, $ArCH_2CH$, J = 11.26 Hz), 2.90 (m, 1, CHN), 2.70 (m, 2, $ArCH_2$), 2.32 (s, 3, $ArCH_3$), 2.13 (m, 1, CH_2CN), 1.88 (m, 1, CH_2CN).

EXAMPLE 3

<u>2-(N-benzyl-N-3-methylbenzoyl)-6,7-dimethoxy-3,4-dihydro-2-naphthylamine (2c).</u> To a solution of 3.504 g (17.0 mmol) of 6,7-dimethoxy-β-tetralone in 100 mL of toluene was added 1.870 g (1.025 equivalents) of benzylamine. The reaction was heated at reflux overnight under N_2 with continuous water removal. The reaction was cooled and the solvent was removed to yield the N-benzyl enamine as a brown oil.

The 3-methylbenzoyl chloride acylating agent was prepared by suspending 3.016 g (22.0 mmol) of 3-toluic acid in 100 mL benzene. To this solution was added 2.0 equivalents (3.84 mL) of oxalyl chloride, dropwise with a pressure-equalizing dropping funnel at O °C. Catalytic DMF (2-3 drops) was added to the reaction mixture and the ice bath was removed. The progress of the reaction was monitored using infrared spectroscopy. The solvent was removed and the residual oil was held under high vacuum overnight.

The resulting N-benzyl enamine residue was dissolved in 100 mL of CH_2Cl_2, and to this solution was added 1.763 g (17.42 mmol) of triethylamine at O °C. The 3-methylbenzoyl chloride (2.759 g, 17.84 mmol) was dissolved in 20 mL CH_2Cl_2 and this solution was added dropwise to the cold, stirring N-benzyl enamine solution. The reaction was allowed to warm to room temperature and was left to stir under N_2 overnight. The reaction mixture was washed successively with 2 X 30 mL of 5% aqueous HCl, 2 X 30 mL of saturated sodium bicarbonate solution, saturated NaCl solution, and was dried over $MgSO_4$. After filtration, the filtrate was concentrated. Crystallization from diethyl ether gave 4.431 g (63.1%) of the enamide **2c**: mp 96-97 °C; CIMS (isobutane, M + 1) 414; ^{1}H-NMR ($CDCl_3$) δ 7.36 (s, 1, ArH), 7.26 (m, 3, ArH), 7.20 (m, 5, ArH), 6.50 (s, 1, ArH), 6.40 (s, 1, ArH), 6.05 (s,

1, ArCH), 4.95 (s, 2, $ArCH_2N$), 3.75 (s, 3, OCH_3), 3.74 (s, 3, OCH_3), 2.43 (t, 2, $ArCH_2$), 2.28 (s, 3, $ArCH_3$), 2.07 (t, 2, CH_2).

Trans-3-methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine-5-one (3c). A solution of 1.922 g (4.65 mmol) of the 6,7-dimethoxyenamide **2c**, in 500 mL of THF, was introduced to an Ace Glass 500 mL photochemical reactor. This solution was stirred while irradiating for 5 hours with a 450 watt Hanovia medium pressure, quartz, mercury-vapor lamp seated in a water-cooled, quartz immersion well. The solution was concentrated and crystallized from diethyl ether to provide 0.835 g (43.4%) of lactam **3c**: mp 154-157 °C; CIMS (isobutane, M + 1) 414; ^{1}H-NMR ($CDCl_3$) δ 7.94 (s, 1, ArH), 7.34 (d, 1, ArH), 7.17 (m, 6, ArH), 6.84 (s, 1, ArH), 6.54 (s, 1, ArH), 5.28 (d, 1, $ArCH_2N$), 4.66 (d, 1, $ArCH_2N$), 4.23 (d, 1, Ar_2CH, J = 11.4 Hz), 3.78 (s, 3, OCH_3), 3.74 (s, 3, OCH_3), 3.61 (m, 1, CHN), 2.59 (m, 2, $ArCH_2$), 2.34 (s, 3, $ArCH_3$), 2.15 (m, 1, CH_2CN), 1.63 (m, 1, CH_2CN).

Trans-3-methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (4c). A solution of 0.773 g (1.872 mmol) of the lactam **3c**, in 50 mL dry THF was cooled in an ice-salt bath and 4.0 equivalents (7.5 mL) of 1.0 molar BH_3 were added through a syringe. The reaction was heated at reflux under N_2 overnight. Methanol (6 mL) was added dropwise to the reaction mixture and reflux was continued for 1 h. The solvent was removed. The residue was chased two times with methanol and twice with ethanol. The residue was placed under high vacuum (0.05 mm Hg) overnight. The residue was dissolved in ethanol and was carefully acidified with concentrated HCl. The volatiles were removed and the product was crystallized from ethanol to afford 0.652 g (80%) of **4c** as the hydrochloride salt: mp 193-195 °C; CIMS (isobutane, M + 1) 400; ^{1}H-NMR ($CDCl_3$, free base) δ 7.38 (d, 2, ArH), 7.33 (m, 2, ArH), 7.28 (m, 2, ArH), 7.07 (d, 1, ArH), 6.90 (s, 1, ArH), 6.88 (s, 1, ArH), 6.72 (s, 1, ArH), 4.02 (d, 1, Ar_2CH, J = 11.2 Hz), 3.90 (d, 1, $ArCH_2N$), 3.87 (s, 3, OCH_3), 3.82 (m, 1, $ArCH_2N$), 3.78 (s, 3, OCH_3), 3.48 (d, 1, $ArCH_2N$), 3.30 (d, 1, $ArCH_2N$), 2.88 (m, 1, $ArCH_2$), 2.82 (m, 1, CHN), 2.36 (m, 1, CH_2CN), 2.32 (s, 3, $ArCH_3$), 2.20 (m, 1, $ArCH_2$), 1.95 (m, 1, CH_2CN).

Trans-3-methyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (5c). A solution of 0.643 g (1.47 mmol) of the 6-benzyl hydrochloride salt **4c** prepared above in 100 mL of 95%

ethanol containing 130 mg of 10% Pd/C catalyst was shaken at room temperature under 50 psig of H_2 for 8 hours. After removal of the catalyst by filtration through Celite, the solution was concentrated to dryness and the residue was recrystallized from acetonitrile to afford 0.397 g (78%) of **5c** as a crystalline salt: mp 254-256 °C; CIMS (isobutane, M + 1) 310; ^{1}H-NMR (DMSO, HCl salt) δ 10.01 (s, 1, NH), 7.36 (d, 1, ArH), 7.09 (d, 1, ArH), 6.98 (s, 1, ArH), 6.92 (s, 1, ArH), 6.74 (s, 1, ArH), 4.04 (s, 2, $ArCH_2N$), 3.88 (s, 3, OCH_3), 3.81 (s, 3, OCH_3), 3.76 (d, 1, Ar_2CH), 2.89 (m, 2, $ArCH_2$), 2.70 (m, 1, CHN), 2.36 (s, 3, $ArCH_3$), 2.16 (m, 1, CH_2CN), 1.70 (m, 1, CH_2CN).

Trans-3-methyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (**6c**). The 10,11-dimethoxy hydrochloride salt **5c** (0.520 g, 1.51 mmol) was converted to its free base. The free base was dissolved in 35 mL of dichloromethane and the solution was cooled to -78 °C. A 1.0 molar solution of BBr_3 (4.0 equivalents, 6.52 mL) was added slowly via syringe. The reaction was stirred under N_2 overnight with concomitant warming to room temperature. Methanol (7.0 mL) was added to the reaction mixture and the solvent was removed. The residue was placed under high vacuum (0.05 mm Hg) overnight. The residue was dissolved in water and was carefully neutralized to its free base initially with sodium bicarbonate and finally with ammonium hydroxide (1-2 drops). The free base was isolated by suction filtration and was washed with cold water. The filtrate was extracted several times with dichloromethane and the organic extracts were dried, filtered, and concentrated. The filter cake and the organic residue were combined, dissolved in ethanol, and carefully acidified with concentrated HCl. After removal of the volatiles, the HCl salt was crystallized as a solvate from methanol to yield 0.341 g (71.3%) or **6c**: mp 190 °C (dec.); CIMS (isobutane, M + 1) 282; ^{1}H-NMR (DMSO, HCl salt) δ 9.55 (s, 1, NH), 8.85 (d, 2, OH), 7.30 (d, 1, ArH), 7.22 (s, 1, ArH), 7.20 (d, 1, ArH), 6.68 (s, 1, ArH), 6.60 (s, 1, ArH), 4.31 (s, 2, $ArCH_2N$), 4.09 (d, 1, $ArCH_2CH$, J = 11.2 Hz), 2.91 (m, 1, CHN), 2.72 (m, 2, $ArCH_2$), 2.35 (s, 3, $ArCH_3$), 2.16 (m, 1, CH_2CN, 1.85 (m, 1, CH_2CN).

EXAMPLE 4

2-(N-benzyl-N-2-methylbenzoyl)-6,7-dimethoxy-3,4-dihydro-2-naphthylamine (**2d**). To a solution of 5.123 g (24.8 mmol) of 6,7-dimethoxy-β-

tetralone in 200 mL of toluene was added 2.929 g (1.025 equivalents) of benzylamine. The reaction was heated at reflux overnight under N_2 with continuous water removal. The reaction was cooled and the solvent was removed to yield the N-benzyl enamine as a brown oil.

The 2-methylbenzoyl chloride acylating agent was prepared by suspending 4.750 g (42.2 mmol) of 2-toluic acid in 100 mL benzene. To this solution was added 2.0 equivalents (7.37 mL) of oxalyl chloride, dropwise via a pressure-equalizing dropping funnel at 0°C. Catalytic DMF (2-3 drops) was added to the reaction mixture and the ice bath was removed. The progress of the reaction was monitored using infrared spectroscopy. The solvent was removed and the residual oil was held under high vacuum overnight.

The resulting N-benzyl enamine residue was dissolved in 100 mL of CH_2Cl_2, and to this solution was added 2.765 g (1.1 equivalent) of triethylamine at O °C. The 2-methylbenzoyl chloride (4.226 g, 27.3 mmol) was dissolved in 25 mL CH_2Cl_2 and this solution was added dropwise to the cold, stirring N-benzyl enamine solution. The reaction was allowed to warm to room temperature and was left to stir under N_2 overnight. The reaction mixture was washed successively with 2 X 30 mL of 5% aqueous HCl, 2 X 30 mL of saturated sodium bicarbonate solution, saturated NaCl solution, and was dried over $MgSO_4$. After filtration, the filtrate was concentrated. The resulting oil was purified via a chromatotron utilizing a 5% ether/dichloromethane eluent mobile phase to yield 3.950 g (38.5%) of **2d** as an oil: CIMS (isobutane, M + 1) 414; 1H-NMR ($CDCl_3$) δ 7.34 (d, 2, ArH), 7.30 (m, 2, ArH), 7.25 (d, 2, ArH), 7.14 (m, 2, ArH), 7.07 (m, 1, ArH), 6.47 (s, 1, ArH), 6.37 (s, 1, ArH), 6.04 (s, 1, ArCH), 4.96 (s, 2, $ArCH_2N$), 3.78 (s, 3, OCH_3), 3.77 (s, 3, OCH_3), 2.39 (s, 3, $ArCH_3$), 2.30 (t, 2, $ArCH_2$), 1.94 (t, 2, CH_2).

Trans-4-methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine-5-one (**3d**). A solution of 2.641 g (6.395 mmol) of the 6,7-dimethoxyenamide **2d**, in 450 mL of THF, was introduced to an Ace Glass 500 mL photochemical reactor. This solution was stirred while irradiating for 3 hours with a 450 watt Hanovia medium pressure, quartz, mercury-vapor lamp seated in a water-cooled, quartz immersion well. The solution was concentrated and crystallized from diethyl ether to provide 0.368 (20%) of the 10,11-dimethoxy lactam **3d**: mp 175-176 °C; CIMS (isobutane, M + 1) 414; 1H-NMR ($CDCl_3$) δ 7.88 (m, 3, ArH),

7.65 (d, 1, ArH), 7.40 (m, 2, ArH), 7.21 (m, 2, ArH), 6.87 (s, 1, ArH), 6.60 (s, 1, ArH), 5.34 (d, 1, $ArCH_2N$), 4.72 (d, 1, $ArCH_2N$), 4.24 (d, 1, Ar_2CH, J = 10.9 Hz), 3.86 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 3.68 (m, 1, CHN), 2.73 (s, 3, $ArCH_3$), 2.64 (m, 2, $ArCH_2$); 2.20 (m, 1, CH_2CN), 1.72 (m, 1, CH_2CN).

<u>Trans-4-methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (4d).</u> A solution of 1.640 g (3.97 mmol) of the lactam **3d**, in 100 mL dry THF was cooled in an ice-salt bath and 4.0 equivalents (15.9 mL) of 1.0 molar BH_3 were added through a syringe. The reaction was heated at reflux under N_2 overnight. Methanol (10 mL) was added dropwise to the reaction mixture and reflux was continued for 1 hour. The solvent was removed and the residue was chased two times with methanol and twice with ethanol. The residue was placed under high vacuum (0.05 mm Hg) overnight. The residue was dissolved in ethanol and was carefully acidified with concentrated HCl. The volatiles were removed and the product was crystallized from ethanol to afford 1.288 g (74.5%) of **4d** as the hydrochloride salt: mp 232-235 °C; CIMS (isobutane, M + 1), 400; ^{1}H-NMR ($CDCl_3$, free base) δ 7.38 (d, 2, ArH), 7.33 (m, 2, ArH), 7.27 (d, 1, ArH), 7.24 (m, 1, ArH), 7.16 (m, 1, ArH), 7.06 (d, 1, ArH), 6.85 (s, 1, ArH), 6.71 (s, 1, ArH), 4.05 (d, 1, Ar_2CH, J = 10.8 Hz), 3.89 (d, 1, $ArCH_2N$), 3.87 (s, 3, OCH_3), 3.82 (m, 1, $ArCH_2N$), 3.76 (s, 3, OCH_3), 3.55 (d, 1, $ArCH_2N$), 3.31 (d, 1, $ArCH_2N$), 2.88 (m, 1, $ArCH_2$), 2.81 (m, 1, CHN), 2.34 (m, 1, CH_2CN), 2.20 (m, 1, $ArCH_2$), 2.17 (s, 3, $ArCH_3$), 1.94 (m, 1, CH_2CN).

<u>Trans-4-methyl-10, 11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (5d).</u> A solution of 0.401 g (0.92 mmol) of the 6-benzyl hydrochloride salt **4d** in 100 mL of 95% ethanol containing 100 mg of 10% Pd/C catalyst was shaken at room temperature under 50 psig of H_2 for 8 hours. After removal of the catalyst by filtration through Celite, the solution was concentrated to dryness and the residue was recrystallized from acetonitrile to afford 0.287 g (90.2%) of **5d** as a crystalline salt: mp 215-216 °C; CIMS (isobutane, M + 1) 310; ^{1}H-NMR ($CDCl_3$, free base) δ 9.75 (s, 1, NH), 7.29 (d, 1, ArH), 7.28 (d, 1, ArH), 7.21 (m, 1, ArH), 6.86 (s, 1, ArH), 6.81 (s, 1, ArH), 4.35 (d, 1, $ArCH_2N$), 4.26 (d, 1, $ArCH_2N$), 4.23 (d, 1, Ar_2CH, J = 11.17 Hz), 3.75 (s, 3, OCH_3), 3.65 (s, 3, OCH_3), 2.96 (m, 1, CHN), 2.83 (m, 2, $ArCH_2$), 2.30 (s, 3, $ArCH_3$), 2.21 (m, 1, CH_2CN), 1.93 (m, 1, CH_2CN).

Trans-4-methyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (**6d**). The 10,11-dimethoxy hydrochloride salt **5d** (0.485 g, 1.40 mmol) was converted to its free base. The free base was dissolved in 35 mL of dichloromethane and the solution was cooled to -78°C. A 1.0 molar solution of BBr_3 (4.0 equivalents, 5.52 mL) was added slowly through a syringe. The reaction was stirred under N_2 overnight with concomitant warming to room temperature. Methanol (7.0 mL) was added to the reaction mixture and the solvent was removed. The residue was placed under high vacuum (0.05 mm Hg) overnight. The residue was dissolved in water and was carefully neutralized to its free base initially with sodium bicarbonate and finally with ammonium hydroxide (1-2 drops). The free base was isolated by suction filtration and was washed with cold water, the filtrate was extracted several times with dichloromethane and the organic extracts were dried, filtered, and concentrated. The filter cake and the organic residue were combined, dissolved in ethanol and carefully acidified with concentrated HCl. After removal of the volatiles, the HCl salt was crystallized as a solvate from methanol to yield 0.364 g (81.6%) of **6d**: mp 195 °C (dec.); CIMS (isobutane, M + 1) 282; ^{1}H-NMR (DMSO, HCl salt) d 9.55 (s, 1, NH), 8.85 (s, 1, OH), 8.80 (s, 1, OH), 7.28 (m, 2, ArH), 7.20 (d, 1, ArH), 6.65 (s, 1, ArH), 6.60 (s, 1, ArH), 4.32 (d, 1, $ArCH_2N$), 4.26 (d, 1, $ArCH_2N$), 4.13 (d, 1, Ar_2CH, J = 11.63 Hz), 2.92 (m, 1, CHN), 2.75 (m, 1, $ArCH_2$), 2.68 (m, 1, $ArCH_2$), 2.29 (s, 3, $ArCH_3$), 2.17 (m, 1, CH_2CN), 1.87 (m, 1, CH_2CN).

EXAMPLE 5

Using the same procedures described in Example 4 herein, trans-2-benzyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (**6e**) was synthesized, except that in the preparation of the precursor **2e**, 2-benzylbenzoyl chloride replaced 4-methylbenzoyl chloride, as described in the preparation of related compound **2d**.

EXAMPLE 6

The affinity of the compounds described in Examples 2, 3, 5, and of dihydrexidine (Example 1) for D_1 and D_2 receptors was assayed utilizing rat brain striatal homogenates having D_1 and D_2 receptors labeled with ^{3}H-SCH 23390 and ^{3}H-spiperone, respectively. The data obtained are shown in Table II.

TABLE II

Compound	D_1 Affinity [(a)]	D_2 Affinity [(a)]	D_1:D_2 Selectivity
6b	14	650	46
6c	7	45	6
6e	290	185	0.6
Dihydrexidine (**6a**)	8	100	13

(a) Affinity in nM.

EXAMPLE 7. Synthesis of 8,9-dihydroxy-1,2,3,11b-tetrahydrochromeno[4,3,2-*de*]isoquinoline hydrobromide (Dinoxyline, **16a**).

1,2-Dimethoxy-3-methoxymethoxybenzene (8). A slurry of sodium hydride was prepared by adding 1000 mL of dry THF to 7.06 g (0.18 mol) of sodium hydride (60% dispersion in mineral oil) under an argon atmosphere at 0 °C. To the slurry, 2,3-dimethoxyphenol (23.64 g, 0.153 mol) was added through a syringe. The resulting solution was allowed to warm to room temperature and stirred for two hours. The resulting black solution was cooled to 0 °C and 13.2 mL of chloromethylmethyl ether (14 g, 0.173 mol) was slowly added with a syringe. The solution was allowed to reach room temperature and stirred for an additional 8 hours. The resulting yellow mixture was concentrated to an oil that was dissolved in 1000 mL of diethyl ether. The resulting solution was washed with water (500 mL), 2N NaOH (3 x 400 mL), dried ($MgSO_4$), filtered, and concentrated. After Kugelrohr distillation (90-100 °C, 0.3 atm), 24.6 g (84%) of **8** as a clear oil was obtained: ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (t, 1H, $J = 8.7$ Hz); 6.79 (dd, 1H, $J = 7.2$, 1.8 Hz); 6.62 (dd, 1H, $J = 6.9$, 1.2 Hz); 5.21 (s, 2H); 3.87 (s, 3H); 3.85 (s, 3H); 3.51 (s, 3H); CIMS *m/z* 199 ($M+H^+$, 50%); 167 ($M+H^+$, CH_3OH, 100%); Anal. Calc'd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.93; H, 7.16.

2-(3,4-Dimethoxy-2-methoxymethoxyphenyl)-4,4,5,5-tetra-methyl-1,3,2-dioxaborolane (9). The MOM-protected phenol **8** (10 g, 0.0505 mol) was dissolved in 1000 mL of dry diethyl ether and cooled to -78 °C. A solution of *n*-butyl lithium (22.2 mL, 2.5 M) was then added with a syringe. The cooling bath was removed and the solution was allowed to warm to room temperature. After stirring the solution at room temperature for two hours, a yellow precipitate was observed.

The mixture was cooled to -78°C, and 15 mL of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.080 mol) was added through a syringe. The cooling bath was removed after two hours. Stirring was continued for four hours at room temperature. The mixture was then poured into 300 mL of water and extracted several times with diethyl ether (3 x 300 mL), dried (Na_2SO_4), and concentrated to **9** a yellow oil (12.37g, 76%) that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, 1H, J = 8.4 Hz); 6.69 (d, 1H, J = 8.4 Hz); 5.15 (s, 2H); 3.87 (s, 3H); 3.83 (s, 3 H); 1.327 (s, 12H).

<u>4-Bromo-5-nitroisoquinoline (11).</u> Potassium nitrate (5.34 g; 0.052 mol) was added to 20 mL of concentrated sulfuric acid and slowly dissolved by careful heating. The resulting solution was added dropwise to a solution of 4-bromoisoquinoline (10 g, 0.048 mol) dissolved in 40 mL of the same acid at 0 °C. After removal of the cooling bath, the solution was stirred for one hour at room temperature. The reaction mixture was then poured onto crushed ice (400 g) and made basic with ammonium hydroxide. The resulting yellow precipitate was collected by filtration and the filtrate was extracted with diethyl ether (3 x 500 mL), dried (Na_2SO_4), and concentrated to give a yellow solid that was combined with the initial precipitate. Recrystallization from methanol gave 12.1 g (89%) of **11** as slightly yellow crystals: mp 172-174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 1H); 8.87 (s, 1H); 8.21 (dd, 1H, J = 6.6, 1.2 Hz); 7.96 (dd, 1 H, J = 6.6 , 1.2 Hz); 7.73 (t, 1 H, J = 7.5 Hz); CIMS *m/z* 253 (M+H$^+$, 100%); 255 (M+H$^+$+2, 100%); Anal. Calc'd for $C_9H_5BrN_2O_2$: C, 42.72; H, 1.99; N, 11.07. Found: C, 42.59; H, 1.76; N, 10.87.

<u>4-(3,4-Dimethoxy-2-methoxymethoxyphenyl)-5-nitroisoquinoline (12).</u> Isoquinoline **11** (3.36 g, 0.0143 mol), pinacol boronate ester **9** (5.562 g, 0.0172 mol), and 1.0 g (6 mol%) of $(Ph_3)Pd$ were suspended in 100 mL of dimethoxyethane (DME). Potassium hydroxide (3.6 g; 0.064 mol), and 0.46 g (10 mol%) of tetrabutylammonium bromide were dissolved in 14.5 mL of water and added to the DME mixture. The resulting suspension was degassed for 30 minutes with argon and then heated at reflux for four hours. The resulting black solution was allowed to cool to room temperature, poured into 500 mL of water, extracted with diethyl ether (3 x 500 mL), dried (Na_2SO_4), and concentrated. The product was then purified by column chromatography (silica gel, 50% ethyl acetate-hexane) giving 5.29 g (80.1%) of **12** as yellow crystals: mp 138-140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H);

8.61 (s, 1H); 8.24 (dd, 1H, J = 7.2, 0.9 Hz); 8.0 (dd, 1H, J = 6.3, 1.2 Hz); 7.67 (t, 1H, J = 7.8 Hz); 7.03 (d, 1H, J = 9.6 Hz); 6.81 (d, 1H, J = 8.1 Hz); 4.86 (d, 1H, J = 6 Hz); 4.70 (d, 1H, J = 5.4 Hz); 3.92 (s, 3H); 3.89 (s, 3 H); 2.613 (s, 3 H); CIMS *m/z* 371 ($M+H^+$, 100%); Anal. Calc'd for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.66; H, 4.90; N, 7.56.

<u>2,3-Dimethoxy-6-(5-nitroisoquinolin-4-yl)phenol (13).</u> After dissolving isoquinoline **12** (5.285 g, 0.014 mol) in 200 mL of methanol by gentle heating, *p*-toluenesulfonic acid monohydrate (8.15 g; 0.043 mol) was added in several portions. Stirring was continued for four hours at room temperature. After completion of the reaction, the solution was made basic by adding saturated sodium bicarbonate. The product was then extracted with CH_2Cl_2 (3 x 250 mL), dried (Na_2SO_4), and concentrated. The resulting **13** as a yellow solid (4.65 g; 98%) was used directly in the next reaction. An analytical sample was recrystallized from methanol: mp 170-174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H); 8.62 (s, 1H); 8.24 (dd, 1H, J = 7.2, 0.9 Hz); 7.99 (dd, 1H, J = 6.3, 1.2 Hz); 7.67 (t, 1H, J = 7.8 Hz); 6.96 (d, 1H, J = 8.7 Hz); 6.59 (d, 1H, J = 8.7 Hz); 5.88 (bs, 1H); 3.94 (s, 3H); 3.92 (s, 3H); CIMS *m/z* 327 ($M+H^+$, 100%); Anal. Calc'd for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.58; Found: C, 62.18; H, 4.38; N, 8.35.

<u>8,9-dimethoxychromeno[4,3,2-*de*]isoquinoline (14).</u> Phenol **13** (4.65 g, 0.014 mol) was dissolved in 100 mL of dry DMF. The solution was degassed with argon for thirty minutes. Potassium carbonate (5.80 g, 0.042 mol) was added to the yellow solution in one portion. After heating at 80 °C for one hour, the mixture had turned brown and no more starting material remained. After the solution was cooled to room temperature, 200 mL of water was added. The aqueous layer was extracted with dichloromethane (3 x 500 mL), this organic extract was washed with water (3 x 500 mL), dried (Na_2SO_4), and concentrated. Isoquinoline **14** was obtained as a white powder (3.65 g 92%) and was used in the next reaction without further purification. An analytical sample was recrystallized from ethyl acetate:hexane: mp 195-196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (s, 1H); 8.82 (s, 1H); 7.87 (d, 1H, J = 8.7 Hz); 7.62 (m, 3H); 7.32 (dd, 1H, J = 6.0, 1.5 Hz); 6.95 (d, J = 9.6 Hz); 3.88 (s, 3H); 3.82 (s, 3H). CIMS *m/ z* 280 ($M+H^+$, 100%).

<u>8,9-dimethoxy-1,2,3,11b-tetrahydrochromeno[4,3,2-*de*]isoquinoline (15a).</u> Platinum (IV) oxide (200 mg) was added to a solution containing 50 mL of

acetic acid and isoquinoline **14** (1 g; 3.5 mmol). After adding 2.8 mL of concentrated HCl, the mixture was shaken on a Parr hydrogenator at 60 psi for 24 hours. The resulting green solution was filtered through Celite to remove the catalyst and the majority of the acetic acid was removed under reduced pressure. The remaining acid was neutralized using a saturated sodium bicarbonate solution, extracted with diethyl ether (3 x 250 mL), dried (Na_2SO_4), and concentrated. The resulting **14** as an oil (0.997 g; 99%) was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (t, 1H, J = 7.5 Hz); 7.00 (d, 1H, J = 8.4 Hz); 6.78 (m, 2H); 6.60 (d, 1H, J = 9 Hz); 4.10 (s, 2H); 3.84 (m, 8H); 2.93 (t, 1H, J = 12.9 Hz).

<u>8,9-dihydroxy-1,2,3,11b-tetrahydrochromeno[4,3,2-*de*]isoquinoline hydrobromide (16a).</u> The dimethoxy derivative **15a** (0.834 g; 3.0 mmol) was dissolved in 50 mL of anhydrous dichloromethane. The solution was cooled to -78 °C and 15.0 mL of a boron tribromide solution (1.0 M in dichloromethane) was slowly added. The solution was stirred overnight, while the reaction slowly warmed to room temperature. The solution was recooled to -78 °C, and 50 mL of methanol was slowly added to quench the reaction. The solution was then concentrated to dryness. Methanol was added and the solution was concentrated. This process was repeated three times. The resulting brown solid was treated with activated charcoal and recrystallized from ethanol to give **16a**: mp 298-302 °C (dec.); ^{1}H NMR (300 MHz, D_2O) δ 7.32 (t, 1H, J = 6.6 Hz); 7.13 (d, 1H, J = 8.4 Hz); 7.04 (d, 1H, J = 8.4 Hz); 4.37 (m, 2H); 4.20 (t, 3H, J = 10 Hz); Anal. Calc'd for $C_{15}H_{14}BrNO_3 \cdot H_2O$: C, 50.87; H, 4.55; N, 3.82. Found: C, 51.18; H, 4.31; N, 3.95.

EXAMPLE 8. *N*-substituted derivatives of dinoxyline.

<u>*N*-allyl-8,9-dimethoxy-1,2,3,11b-tetrahydrochromeno[4,3,2-*de*]isoquinoline (15b).</u> Tetrahydroisoquinoline **15a** (1.273 g; 4.5 mmol) was dissolved in 150 mL of acetone. Potassium carbonate (0.613 g; 4.5 mmol) and 0.4 mL (4.6 mmol) of allyl bromide were added. The reaction was stirred at room temperature for four hours. The solid was then removed by filtration and washed on the filter several times with ether. The filtrate was concentrated and purified by flash chromatography (silica gel, 50% ethyl acetate-hexane) to give 1.033 g (71%) of **15b** a yellow oil that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, 1H, J = 9 Hz); 7.04 (d, 1H, J = 9 Hz); 6.83 (m, 2H); 6.65 (d, 1H, J = 6 Hz);

5.98 (m, 1H); 5.27 (m, 2H); 4.10 (m, 3H); 3.95 (s, 3H); 3.86 (s, 3H); 3.46 (d, 1H, J = 15 Hz); 3.30 (d, 2H, J = 6 Hz); 2.56 (t, 1H, J = 12 Hz).

N-allyl-8,9-dihydroxy-1,2,3,11b-tetrahydrochromeno[4,3,2-*de*]isoquinoline (**16b**). *N*-Allylamine **15b** (0.625 g; 1.93 mmol) was dissolved in 50 mL of dichloromethane. The solution was cooled to -78 °C and 10.0 mL of BBr_3 solution (1.0 M in dichloromethane) was slowly added. The solution was stirred overnight, while the reaction slowly warmed to room temperature. After recooling the solution to -78 °C, 50 mL of methanol was slowly added to quench the reaction. The reaction was then concentrated to dryness. Methanol was added and the solution was concentrated. This process was repeated three times. Recystallization of the resulting brown solid from ethanol gave 0.68 g (61%) of **16b** as a white solid: mp 251-253 °C (dec.); ^{1}H NMR (300 MHz, D_2O) δ 10.55 (s, 1H); 10.16 (s, 1H); 8.61 (t, 1H, J = 9 Hz); 8.42 (d, 1H, J = 9 Hz); 8.31 (d, 1H, J = 9 Hz); 7.87 (d, 1H, J = 9 Hz); 7.82 (d, 1H, J = 9 Hz); 7.36 (q, 1H, J = 9 Hz); 6.89 (m, 2H); 6.85 (d, 1H, J = 15 Hz); 5.58 (m, 3H); 5.28 (m, 2H); 3.76 (d, 1H, J = 3 Hz). HRCIMS *m/z* Calc'd: 295.1208; Found: 295.1214.

N-propyl-8,9-dimethoxy-1,2,3,11b-tetrahydrochromeno[4,3,2-*de*]isoquinoline (**15c**). *N*-Allylamine **15b** (1.033 g; 3.2 mmol) was dissolved in 50 mL of ethanol. Palladium on charcoal (10% dry; 0.103 g) was then added. The mixture was shaken on a Parr hydrogenator under 60 psi H_2 for 3 hours. After TLC showed no more starting material, the mixture was filtered through Celite and concentrated to give 0.95 g (91%) of **15c** as an oil that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, 1H, J = 7.2 Hz); 7.04 (d, 1H, J = 8.1 Hz); 6.84 (t, 2H, J = 7.5 Hz); 6.65 (d, 1H, J = 8.4 Hz); 4.07 (m, 2H); 3.95 (s, 3H); 3.86 (s, 3H); 3.71 (q, 1H, J = 5.1 Hz); 3.42 (d, 2H, J = 15.6 Hz); 2.62 (m, 2H); 2.471 (t, J = 10.5 Hz); 1.69 (h, 2H, J = 7.2 Hz); 0.98 (t, 3H, J = 7.5 Hz); CIMS *m/z* 326 ($M+H^+$, 100%).

N-propyl-8,9-dihydroxy-1,2,3,11b-tetrahydrochromeno[4,3,2-*de*]isoquinoline (**16c**). The *N*-propyl amine **15c** (0.90 g; 2.8 mmol) was dissolved in 200 mL of dichloromethane and cooled to -78 °C. In a separate 250 mL round bottom flask, 125 mL of dry dichloromethane was cooled to -78 °C, and 1.4 mL (14.8 mmol) of BBr_3 was added through a syringe. The BBr_3 solution was transferred using a cannula to the flask containing the starting material. The solution was stirred

overnight, while the reaction slowly warmed to room temperature. After recooling the solution to -78 °C, 50 mL of methanol was slowly added to quench the reaction. The reaction was then concentrated to dryness. Methanol was added and the solution was concentrated. This process was repeated three times. The resulting tan solid was suspended in hot isopropyl alcohol. Slowly cooling to room temperature resulted in a fine yellow precipitate. The solid was collected by filtration to give **16c** (0.660 g; 63%): mp 259-264 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, 1H, J = 9 Hz); 6.97 (d, 1H, J = 12 Hz); 6.83 (d, 1H, J = 9 Hz); 6.55 (d, 1H, J = 9 Hz); 6.46 (d, 1H, J = 9 Hz); 4.45 (d, 1H, J = 15 Hz); 4.10 (m, 3H); 3.17 (q, 2H, J = 6 Hz); 3.04 (t, 1H, J = 9 Hz); 1.73 (q, 2H, J = 9 Hz); 0.90 (t, 3H, J = 6 Hz); Anal. Calc'd. for $C_{18}H_{20}BrNO_3$: C, 57.16; H, 5.33; N, 3.70. Found: C, 56.78; H, 5.26; N, 3.65.

EXAMPLE 9. Preparation of 2-methyl-2,3-dihydro-4(1*H*)-isoquinolone.

Ethyl 2-bromomethylbenzoate (**18**). A solution of ethyl 2-toluate (**17**, 41.2 g, 0.25 mole) in carbon tetrachloride (200 mL) was added dropwise to a stirring mixture of benzoyl peroxide (100 mg), carbon tetrachloride (200 mL), and NBS (44.5 g, 0.25 mole) at 0 °C. The mixture was heated at reflux for 3.5 h under nitrogen, and allowed to cool to room temperature overnight. The precipitated succinimide was removed by filtration and the filter cake was washed with carbon tetrachloride. The combined filtrates were washed successively with 2 N NaOH (100 mL), and water (2 x 100 mL), and the solution was dried over anhydrous $MgSO_4$, filtered (Celite), and evaporated under vacuum to yield an oil. Drying under high vacuum overnight afforded 60.5 g (99%) of compound **18**: ^{1}H NMR of the product showed the presence of ca. 15% of unreacted **17**. The mixture was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.43 (t, J = 7 Hz, 3H, CH_2 CH_3), 4.41 (q, J = 7 Hz, 2H, CH_2CH_3), 4.96 (s, 1H, CH_2Br), 7.24 (m, 1H, ArH), 7.38 (m, 1H, ArH), 7.48 (m, 2H, ArH).

N-(2-carboethoxy)sarcosine ethyl ester (**19**). To a mixture of sarcosine ethyl ester hydrochloride (32.2 g, 0.21 mole), potassium carbonate (325 mesh; 86.9 g, 0.63 mole), and acetone (800 mL) was added a solution of compound **18** (60.7 g, ca. 0.21 mole, 85:15 **18/17**) in acetone (100 mL) at room temperature under N_2. The mixture was stirred at reflux for 2 h and then left at room temperature for 20 h. The solid was removed by filtration (Celite) and the residue was washed with acetone.

The filtrates were combined and evaporated to afford an oil. The oil was dissolved in 250 mL of 3 N HCl and washed with ether. The aqueous layer was basified with aqueous $NaHCO_3$, and extracted with ether (3 x 250 mL). Evaporation of the ether solution yielded an oil that was vacuum distilled to afford 45.33 g (77%) of compound **19**: bp 140-142 °C/0.5 mm Hg; bp 182-183 °C/10 mm Hg; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H, J = 7.1 Hz, CH_3), 1.36 (t, 3H, J = 7.1 Hz, CH_3), 2.35 (s, 3H, NCH_3), 3.27 (s, 2H, CH_2Ar), 4.00 (s, 2H, NCH_2), 4.14 (q, 2H, J = 7.1 Hz, CH_2CH_3), 4.32 (q, 2H, J = 7.1 Hz, CH_2CH_3), 7.28 (t, 1H, J = 7.4 Hz, ArH), 7.42 (t, 1H, J = 7.6 Hz, ArH), 7.52 (d, 1H, J = 7.8 Hz, ArH), 7.74 (d, 1H, J = 7.7 Hz, ArH).

<u>2-Methyl-2,3-dihydro-4(1*H*)isoquinolone (**20**).</u> Freshly cut sodium (10.9 g, 0.47 g-atom) was added to absolute ethanol (110 mL) under nitrogen and the reaction was heated at reflux. After the metallic sodium had disappeared, a solution of compound **19** (35.9 g, 0.128 mole) in dry toluene (160 mL) was added slowly to the reaction mixture. It was then heated at reflux and ethanol was separated azeotropically via a Dean Stark trap. After cooling, the solvent was evaporated under reduced pressure. The remaining yellow semi-solid residue was dissolved in a mixture of water (50 mL), 95% ethanol (60 mL), and concentrated HCl (240 mL), and heated at reflux for 26 h. After cooling, the mixture was concentrated under vacuum and carefully basified with solid $NaHCO_3$. The basic solution was extracted with ether, dried ($MgSO_4$), and evaporated to an oil that was distilled to afford compound **20** (17.11 g, 83%): bp 130-132 °C/5 mm Hg; bp 81-83 °C/0.4 mm Hg; mp (HCl salt) 250 °C; IR (neat) 1694 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (s, 3H, CH_3), 3.31 (s, 2H, CH_2), 3.74 (s, 2 H, CH_2), 7.22 (d, 1H, J = 7.7 Hz, ArH), 7.34 (t, 1H, J = 7.9 Hz, ArH), 7.50 (t, 1H, J = 7.5 Hz, ArH), 8.02 (d, 1H, J = 7.9 Hz, ArH).

EXAMPLE 10. Synthesis of 8,9-dihydroxy-2,3,7,11b-tetrahydro-1*H*-naphtho[1,2,3-*de*]isoquinoline (dinapsoline, **29**).

<u>2',3'-Dihydro-4,5-dimethoxy-2'-methylspiro[isobenzofuran-1(3*H*),4'(1'*H*)-isoquinoline]-3-one (**22**).</u> To a solution of 2,3-dimethoxy-*N,N'*-diethylbenzamide (**21**, 14.94 g, 63 mmol) in ether (1400 mL) at -78 °C under nitrogen was added sequentially, dropwise, *N,N,N',N'*-tetramethylenediamine (TMEDA, 9.45 mL, 63 mmol), and *sec*-butyllithium (53.3 mL, 69 mmol, 1.3 M solution in hexane). After 1 h, freshly distilled compound **20** (10.1 g, 62.7 mmol) was added to the

heterogenous mixture. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature over 9 h. Saturated NH_4Cl solution (400 mL) was then added and the mixture was stirred for 15 min. The ether layer was separated and the water layer was extracted with dichloromethane (4 x 100 mL). The organic layers were combined, dried ($MgSO_4$), and evaporated to a brown oil. The oil was dissolved in toluene (500 mL), and heated at reflux for 8 h with 3.0 g of *p*-toluene sulfonic acid, cooled, and concentrated under vacuum. The residue was dissolved in dichloromethane, washed with dilute aqueous $NaHCO_3$, water, and then dried (Na_2SO_4), filtered, and evaporated to a gummy residue. On trituration with ethyl acetate/hexane (50:50), a solid precipitated. Recrystallization from ethyl acetate/hexane afforded 12.75 g (63%) of compound **22**: mp 193-194 °C; IR (KBr) 1752 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H, NCH_3), 2.88 (d, 1H, J = 11.6 Hz), 3.02 (d, 1H, J = 11.7 Hz), 3.76 (d, 1H, J = 15.0 Hz), 3.79 (d, 1H, J = 15.1 Hz), 3.90 (s, 3H, OCH_3), 4.17 (s, 3H, OCH_3), 6.83 (d, 1H, J = 8.4 Hz, ArH), 7.03 (d, 1H, J = 8.2 Hz, ArH), 7.11 (m, 3H, ArH), 7.22 (m, 1H, ArH); MS (CI) *m/z* 326 (100).

<u>2',3'-Dihydro-4,5-dimethoxyspiro[isobenzofuran-1(3*H*),4'(1'*H*)-isoquinoline]-3-one (**23**).</u> 1-chloroethyl chloroformate (5.1 mL, 46.3 mmol) was added dropwise to a suspension of compound **22** (6.21 g, 19.2 mmol) in 100 mL of 1,2-dichloroethane at 0 °C under nitrogen. The mixture was stirred for 15 min at 0 °C, and then heated at reflux for 8 h. The mixture was cooled, and concentrated under reduced pressure. To this mixture was added 75 mL of methanol and the reaction was heated at reflux overnight. After cooling, the solvent was evaporated to afford the hydrochloride salt of compound **23** in nearly quantitative yield. It was used in the next step without further purification: mp (HCl salt) 220-222 °C; mp (free base) 208-210 °C; IR (CH_2Cl_2, free base) 1754 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, free base) δ 3.18 (d, 1H, J = 13.5 Hz), 3.30 (d, 1H, J = 13.5 Hz), 3.84 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.02 (s, 2H, CH_2N), 6.67 (d, 1H, J = 7.5 Hz, ArH), 7.12 (m, 2H, ArH), 7.19 (d, 1H, J = 7.5 Hz, ArH), 7.26 (t, 1H, J = 7.5 Hz, ArH), 7.41 (d, 1H, J = 8.5 Hz, ArH); MS (CI) *m/z* 312 (100); HRCIMS Calc'd for $C_{18}H_{17}NO_4$: 312.1236; Found 312.1198; Anal. Calc'd for $C_{18}H_{17}NO_4$: C, 69.44. Found: C, 68.01.

<u>2',3'-Dihydro-4,5-dimethoxy-2'-*p*-toluenesulfonylspiro[isobenzofuran-1(3*H*),4'(1'*H*)isoquinoline]-3-one (**24**).</u> Triethylamine (7 mL) was added dropwise to a mixture of *p*-toluenesulfonyl chloride (3.6 g, 18.9 mmole), compound **23** (as the

HCl salt, obtained from 19.2 mmol of compound **22**), and chloroform (100 mL) at 0 °C under nitrogen. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for 1 h. It was then acidified with 100 mL of cold aqueous 0.1 N HCl, extracted with dichloromethane (2 x 100 mL), and the organic extract was dried ($MgSO_4$), filtered, and evaporated to afford a viscous liquid that on trituration with ethyl acetate/hexane at 0 °C gave a solid. Recrystallization from ethyl acetate/hexane afforded 8.74 g (97%, overall from compound **22**) of compound **24**: mp 208-210 °C; IR (KBr) 1767 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.43 (s, 1H, CH_3), 3.22 (d, 1H, J = 11 Hz), 3.88 (d, 1H, J = 11 Hz), 3.90 (s, 3H, OCH_3), 3.96 (d, 1H, J = 15 Hz), 4.17 (s, 3H, OCH_3), 4.81 (d, 1H, J = 15 Hz), 6.97 (d, 1H, J = 7.7 Hz, ArH), 7.16 (m, 3H, ArH), 7.26 (m, 1H, ArH), 7.38 (d, 2H, J = 8 Hz, ArH), 7.72 (d, 2H, J = 8 Hz, ArH); MS (CI) *m/z* 466 (100).

3,4-Dimethoxy-6-[(2-*p*-toluenesulfonyl-1,2,3,4-tetrahydroisoquinoline)-4-yl]benzoic acid (**25**). A solution of compound **24** (2.56 g, 5.51 mmol) in glacial acetic acid (250 mL) with 10% palladium on activated carbon (6.30 g) was shaken on a Parr hydrogenator at 50 psig for 48 h at room temperature. The catalyst was removed by filtration, and the solvent was evaporated to afford 2.55 g (99%) of compound **25**. An analytical sample was recrystallized from ethanol/water: mp 182-184 °C; IR (KBr) 1717 cm^{-1} (COOH); ^1H NMR (DMSO-d_6) δ 2.35 (s, 3 H, CH_3), 3.12 (m, 1H), 3.51 (dd, 1H, J = 5, 11.5 Hz), 3.71 (s, 6H, OCH_3), 4.10 (m, 1H, Ar_2CH), 4.23 (s, 2H, $ArCH_2N$), 6.52 (d, 1H, J = 7.5 Hz, ArH), 6.78 (d, 1H, J = 7.5 Hz, ArH), 6.90 (m, 1H, ArH), 7.07 (t, 1H, J = 8 Hz, ArH), 7.14 (t, 1H, J = 6.5 Hz, ArH), 7.20 (d, 1H, J = 7.5 Hz, ArH), 7.38 (d, 2H, J = 8 Hz, ArH), 7.63 (d, 2H, J = 8.5 Hz, ArH); MS (CI) *m/z* 468 (16), 450 (63), 296 (100); HRCIMS Calc'd for $C_{25}H_{25}NO_6S$: 468.1481; Found: 468.1467.

2-*N*-*p*-Toluenesulfonyl-4-(2-hydroxymethyl-3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**26**). To a solution of compound **25** (1.4 g, 2.99 mmol) in dry THF (30 mL) was added 1.0 M borane-tetrahydrofuran (8 mL) at 0 °C under N_2. After the addition was complete the mixture was stirred at reflux overnight. Additional borane-tetrahydrofuran (4 mL) was added and stirring was continued for another 30 min. After cooling and evaporating under reduced pressure, methanol (30 mL) was carefully added, and the solvent was removed at low pressure. The process was repeated three times to ensure the methanolysis of the intermediate borane

complex. Evaporation of the solvent gave 1.10 g (81%) of compound **26**. An analytical sample was purified by flash chromatography (silica gel, EtOAc/Hexane) followed by recrystallization from ethyl acetate/hexane: mp 162-164 °C; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H, CH_3), 3.18 (dd, 1H, J = 7.5, 11.9 Hz), 3.67 (dd, 1H, J = 4.5, 11.8 Hz), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.27 (d, 1H, J = 15 Hz), 4.40 (d, 1H, J = 15 Hz), 4.57 (t, 1H, J = 6 Hz, $CHAr_2$), 4.71 (s, 2H, CH_2OH), 6.58 (d, 1H, J = 8.5 Hz, ArH), 6.74 (d, 1H, J = 8.6 Hz, ArH), 6.84 (d, 1H, J = 7.7 Hz, ArH), 7.08 (t, 2H, J = 7.6 Hz, ArH), 7.14 (t, 1H, J = 6.6 Hz, ArH), 7.27 (d, 2H, J = 8 Hz, ArH), 7.65 (d, 2H, J = 8 Hz, ArH); MS (CI) *m/z* 454 (2.57), 436 (100).

8,9-Dimethoxy-2-*p*-toluenesulfonyl-2,3,7,11b-tetrahydro-1*H*-napth[1,2,3-*de*]isoquinoline (27). Powdered compound **26** (427 mg, 0.98 mmol) was added in several portions to 50 mL of cold concentrated sulfuric acid (50 mL) at -40 °C under nitrogen with vigorous mechanical stirring. After the addition, the reaction mixture was warmed to -5 °C over 2 h and then poured onto crushed ice (450 g) and left stirring for 1 h. The product was extracted with dichloromethane (2 x 150 mL), washed with water (2 x 150 mL), dried ($MgSO_4$), filtered, and evaporated to afford an oil that on trituration with ether at 0 °C yielded compound **27** (353 mg, 82%) as a white solid that was used without further purification. An analytical sample was prepared by centrifugal rotary chromatography using 50% EtOAc/hexane as the eluent followed by recrystallization from EtOAc/hexane: mp 204-206 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H, CH_3), 2.80 (m, 1H, H-1a), 3.50 (dd, 1H, J = 4.5, 17.5 Hz, H-1b), 3.70 (dd, 1H, J = 7, 14 Hz, H-3a), 3.828 (s, 3H, OCH_3), 3.832 (s, 3H, OCH_3), 3.9 (m, 1H, H-11b), 4.31 (d, 1H, J = 17.6 Hz, H-7a), 4.74 (ddd, 1H, J = 1.7, 6.0, 11.2 Hz, H-7b), 4.76 (d, 1H, J = 14.8 Hz, H-3b), 6.77 (d, 1H, J = 8.3 Hz, ArH), 6.87 (d, 1H, J = 8.4 Hz, ArH), 6.94 (d, 1H, J = 7.6 Hz, ArH), 7.13 (t, 1H, J = 7.5 Hz, Ar-H-5), 7.18 (d, 1H, J = 7.2 Hz, ArH), 7.33 (d, 2H, J = 8.1 Hz, ArH), 7.78 (d, 2H, J = 8.2 Hz, ArH); MS (CI) *m/z* 436 (55), 198 (86), 157 (100); HRCIMS Calc'd for $C_{25}H_{25}NO_4S$: 436.1583; Found: 436.1570.

8,9-Dimethoxy-2,3,7,11b-tetrahydro-1*H*-napth[1,2,3-*de*]isoquinoline (28). A mixture of compound **27** (440 mg, 1.01 mmol), dry methanol (10 mL) and disodium hydrogen phosphate (574 mg, 4.04 mmol) was stirred under nitrogen at room temperature. To this mixture was added 6.20 g of 6% Na/Hg in three portions

and the reaction was heated at reflux for 2 h. After cooling, water (200 mL) was added and the mixture was extracted with ether (3 x 200 mL). The ether layers were combined, dried ($MgSO_4$), filtered (Celite), and evaporated to give an oil that solidified under vacuum. After rotary chromatography 142 mg (50%) of compound **28** was obtained as an oil. The oil quickly darkened on exposure to air and was used immediately. A small portion of the oil was treated with ethereal HCl and the hydrochloride salt of compound **28** was recrystallized from ethanol/ether: mp (HCl salt) 190 °C (dec.); ^{1}H NMR ($CDCl_3$, free base) δ 3.13 (dd, 1H, J = 10.8, 12 Hz, H-1a), 3.50 (dd, 1H, J = 3.4, 17.4 Hz, H-1b), 3.70 (m, 1H, H-11b), 3.839 (s, 3H, OCH_3), 3.842 (s, 3H, OCH_3), 4.03 (dd, 1H, J = 6, 12 Hz, H-7a), 4.08 (s, 2H, H-3), 4.33 (d, 1H, J = 17.4 Hz, H-7b), 6.78 (d, 1H, J = 8.24 Hz, ArH), 6.92 (m, 3H, ArH), 7.11 (t, 1H, J = 7.5 Hz, ArH), 7.18 (d, 1H, J = 7.5 Hz, ArH); MS (CI) *m/z* 282 (100); HRCIMS Calc'd for $C_{18}H_{19}NO_2$: 282.1494; Found: 282.1497.

<u>8,9-Dihydroxy-2,3,7,11b-tetrahydro-1*H*-napth[1,2,3-*de*]isoquinoline (29).</u> To a solution of compound **28** (25 mg, 0.089 mmole) in dichloromethane (5 mL) at -78 °C was added boron tribromide (0.04 mL, 0.106 g, 0.42 mmol). After stirring at -78 °C under N_2 for 2 h, the cooling bath was removed and the reaction mixture was left stirring at room temperature for 5 h. It was then cooled to -78 °C and methanol (2 mL) was carefully added. After stirring for 15 min at room temperature, the solvent was evaporated. More methanol was added and the process was repeated three times. The resulting gray solid was recrystallized from ethanol/ethyl acetate to yield a total of 12 mg (41%) of the hydrobromide salt of compound **29**: mp 258 °C (dec); ^{1}H NMR (HBr salt, CD_3OD) δ 3.43 (t, 1H, J = 12 Hz, H-1a), 3.48 (dd, 1H, J = 3.5, 18 Hz, H-1b), 4.04 (m, 1H, H-11b), 4.38 (dd, 2H, J = 5.5, 12 Hz, H-7), 4.44 (s, 2H, H-3), 6.58 (d, 1H, J = 8.5 Hz, ArH), 6.71 (d, 1H, J = 8.5 Hz, ArH), 7.11 (d, 1H, J = 7.5 Hz, ArH), 7.25 (t, 1H, J = 7.5 Hz, ArH), 7.32 (d, 1H, J = 7.5 Hz, ArH); MS (CI) *m/z* 254 (100); HRCIMS Calc'd for $C_{16}H_{15}NO_2$: 254.1181; Found: 254.1192.

WHAT IS CLAIMED IS:

1. A method for treating a patient having a neurological disorder, said method comprising the steps of:

administering to the patient an effective amount of a full D_1 dopamine receptor agonist wherein the dopamine agonist is a compound selected from the group consisting of hexahydrobenzophenanthridines, hexahydrothienophenanthridines, phenylbenzodiazepines, chromenoisoquinolines, naphthoisoquinolines, pharmaceutically acceptable salts thereof, and combinations thereof; and

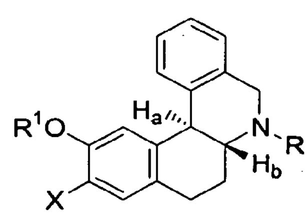
administering to the patient an effective amount of a D_2 dopamine receptor antagonist.

2. The method of claim 1 wherein the dopamine receptor agonist is selective for a D_1 dopamine receptor subtype.

3. The method of claim 1 wherein the dopamine receptor agonist exhibits activity at both the D_1 and D_2 dopamine receptor subtypes.

4. The method of claim 1 wherein the dopamine receptor agonist is about equally selective for the D_1 and D_2 dopamine receptor subtypes.

5. The method of claim 1 wherein the dopamine receptor agonist is a compound having the formula:



wherein:

H_a and H_b are *trans* across the ring fusion bond;

R is hydrogen or C_1-C_4 alkyl;

R^1 is hydrogen, acyl, benzoyl, pivaloyl, or an optionally substituted phenyl protecting group;

X is hydrogen, fluoro, chloro, bromo, or iodo, or

X is a group having the formula $-OR^2$ wherein R^2 is hydrogen, C_1-C_4 alkyl, benzoyl, pivaloyl, or an optionally substituted phenyl protecting group; or the groups R^1 and R^2 are taken together to form a divalent radical having the formula $-CH_2-$ or $-(CH_2)_2-$;

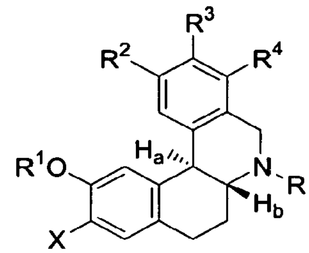
or a pharmaceutically acceptable salt thereof.

6. The method of claim 5 wherein R is hydrogen or methyl, R^1 is hydrogen, X is hydrogen, bromo, or $-OR^2$, and R^2 is hydrogen.

7. The method of claim 5 wherein R is methyl, and X is bromo.

8. The method of claim 5 wherein R is methyl, and X is hydrogen.

9. The method of claim 1 wherein the dopamine receptor agonist is a compound having the formula:



wherein:

H_a and H_b are *trans* across the ring fusion bond;

R is hydrogen or C_1-C_4 alkyl;

R^1 is hydrogen, acyl, benzoyl, pivaloyl, an optionally substituted phenyl protecting group;

X is hydrogen, fluoro, chloro, bromo, iodo, or

X is a group having the formula $-OR^5$ wherein R^5 is hydrogen, C_1-C_4 alkyl, acyl, benzoyl, pivaloyl, an optionally substituted phenyl protecting group; or the groups R^1 and R^5 are taken together to form a divalent radical having the formula $-CH_2-$ or $-(CH_2)_2-$; and

R^2, R^3, and R^4 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, phenyl, fluoro, chloro, bromo, iodo, and a group $-OR^6$ wherein R^6 is hydrogen, acyl, benzoyl, pivaloyl, or an optionally substituted phenyl protecting group,

provided that at least one of R^2, R^3, and R^4 is other than hydrogen;

or a pharmaceutically acceptable salt thereof.

10. The method of claim 9 wherein at least one of the groups R^2, R^3, and R^4 is methyl.

11. The method of claim 9 wherein X is hydroxy.

12. The method of claim 9 wherein R is hydrogen.

13. The method of claim 9 wherein R is C_1-C_4 alkyl.

14. The method of claim 9 wherein R is methyl.

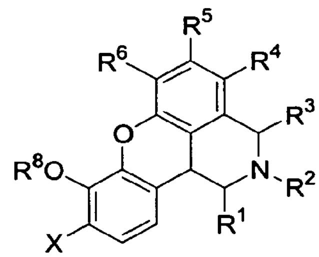
15. The method of claim 9 wherein R is *n*-propyl.

16. The method of claim 9 wherein R is hydrogen, R^2 is methyl, R^3 and R^4 are each hydrogen, R^1 is hydrogen, and X is hydroxy.

17. The method of claim 9 wherein R and R^1 are each hydrogen, X is hydroxy, R^3 is methyl, and R^2 and R^4 are each hydrogen.

18. The method of claim 9 wherein R and R^1 are each hydrogen, X is hydroxy, R^4 is methyl, and R^2 and R^3 are each hydrogen.

19. The method of claim 1 wherein the dopamine receptor agonist is a compound having the formula:



wherein:

R^1, R^2, and R^3 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl and C_2-C_4 alkenyl;

R^4, R^5, and R^6 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, phenyl, halo, and a group having the formula -OR, where R is hydrogen, acyl, benzoyl, pivaloyl, or an optionally substituted phenyl protecting group;

R^8 is hydrogen, C_1-C_4 alkyl, acyl, or an optionally substituted phenyl protecting group;

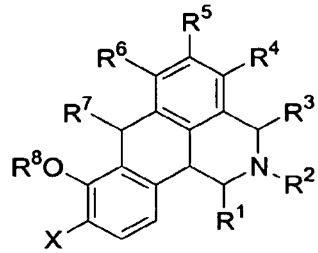
X is hydrogen or halo, or

X is a group having the formula $-OR^9$, where R^9 is hydrogen, C_1-C_4 alkyl, acyl, or an optionally substituted phenyl protecting group; or

when X is a group having the formula $-OR^9$, R^8 and R^9 are taken together to form a divalent group having the formula $-CH_2-$;

or a pharmaceutically acceptable salt thereof.

20. The method of claim 1 wherein the dopamine receptor agonist is a compound having the formula:



wherein:

R^1, R^2, and R^3 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, and C_2-C_4 alkenyl;

R^4, R^5, and R^6 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, phenyl, halogen, and a group having the formula -OR, where R is hydrogen, acyl, benzoyl, pivaloyl, or an optionally substituted phenyl protecting group;

R^7 is selected from the group consisting of hydrogen, hydroxy, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkoxy, and C_1-C_4 alkylthio;

R^8 is hydrogen, C_1-C_4 alkyl, acyl, or an optionally substituted phenyl protecting group; and

X is hydrogen, fluoro, chloro, bromo, or iodo;

and pharmaceutically acceptable salts thereof.

21. The method of any of claims 1 through 20 wherein the D_2 dopamine receptor antagonist is an antipsychotic agent.

22. The method of any of claims 1 through 20 wherein the D_1 dopamine receptor agonist and the D_2 dopamine receptor antagonist are administered to the patient in the same composition.

23. The method of any of claims 1 through 20 wherein the D_1 dopamine receptor agonist and the D_2 dopamine receptor antagonist are administered to the patient in different compositions.

24. The method of any of claims 1 through 20 wherein the D_1 dopamine receptor agonist is a full D_1 dopamine receptor agonist.

25. A pharmaceutical composition comprising a D_1 dopamine receptor agonist wherein the dopamine agonist is a compound selected from the group consisting of hexahydrobenzophenanthridines, hexahydrothienophenanthridines, phenylbenzazepines, chromenoisoquinolines, naphthoisoquinolines, pharmaceutically

acceptable salts thereof, and combinations thereof, and a D_2 dopamine receptor antagonist.

26. A pharmaceutical composition comprising a full D_1 dopamine receptor agonist wherein the dopamine agonist is a compound selected from the group consisting of hexahydrobenzophenanthridines, hexahydrothienophenanthridines, phenylbenzazepines, chromenoisoquinolines, naphthoisoquinolines, pharmaceutically acceptable salts thereof, and combinations thereof, and a D_2 dopamine receptor antagonist.

ABSTRACT OF THE DISCLOSURE

A method for treating a patient having a neurological disorder is described comprising the steps of administering to the patient an effective amount of a partial or full D_1 dopamine receptor agonist, and administering to the patient an effective amount of a D_2 dopamine receptor antagonist. A pharmaceutical composition comprising a D_1 dopamine receptor agonist and a D_2 dopamine receptor antagonist is also described. The dopamine receptor agonist can be selective for D_1 dopamine receptors or can exhibit activity at both D_1 and D_2 dopamine receptors. The D_1 dopamine receptor agonist is illustratively an hexahydrobenzophenanthridine, hexahydrothienophenanthridine, phenylbenzazepine, chromenoisoquinoline, naphthoisoquinoline, pharmaceutically acceptable salt thereof, or combination thereof. The D_2 dopamine receptor antagonist is illustratively any typical or atypical antipsychotic agent, or combination thereof. The D_1 dopamine receptor agonist and the D_2 dopamine receptor antagonist can be administered to the patient in the same or in a different composition or compositions.

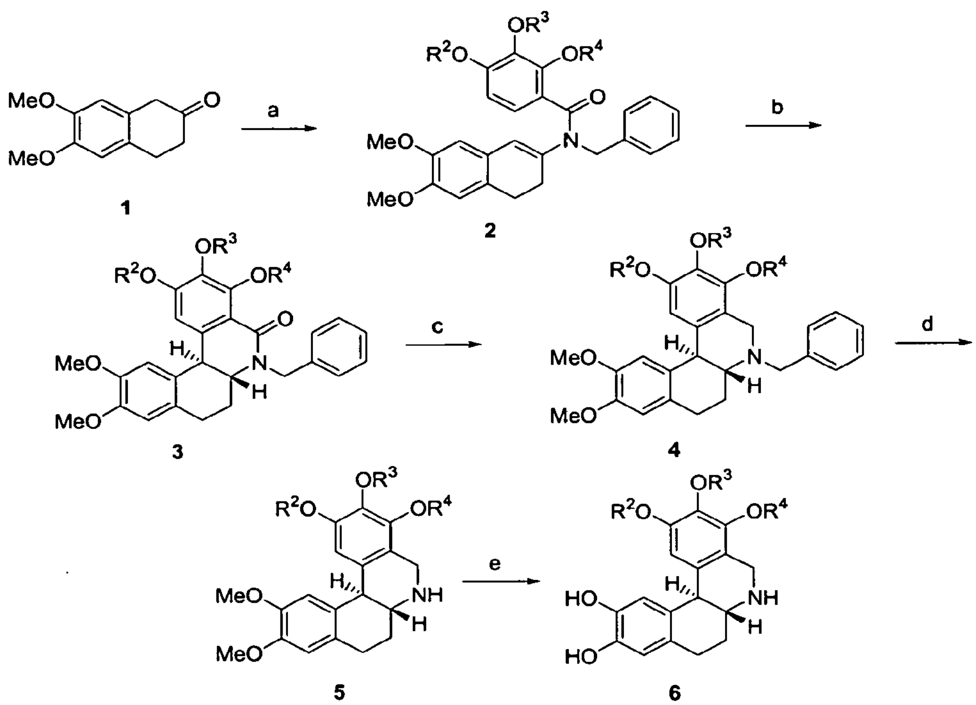


Fig. 1

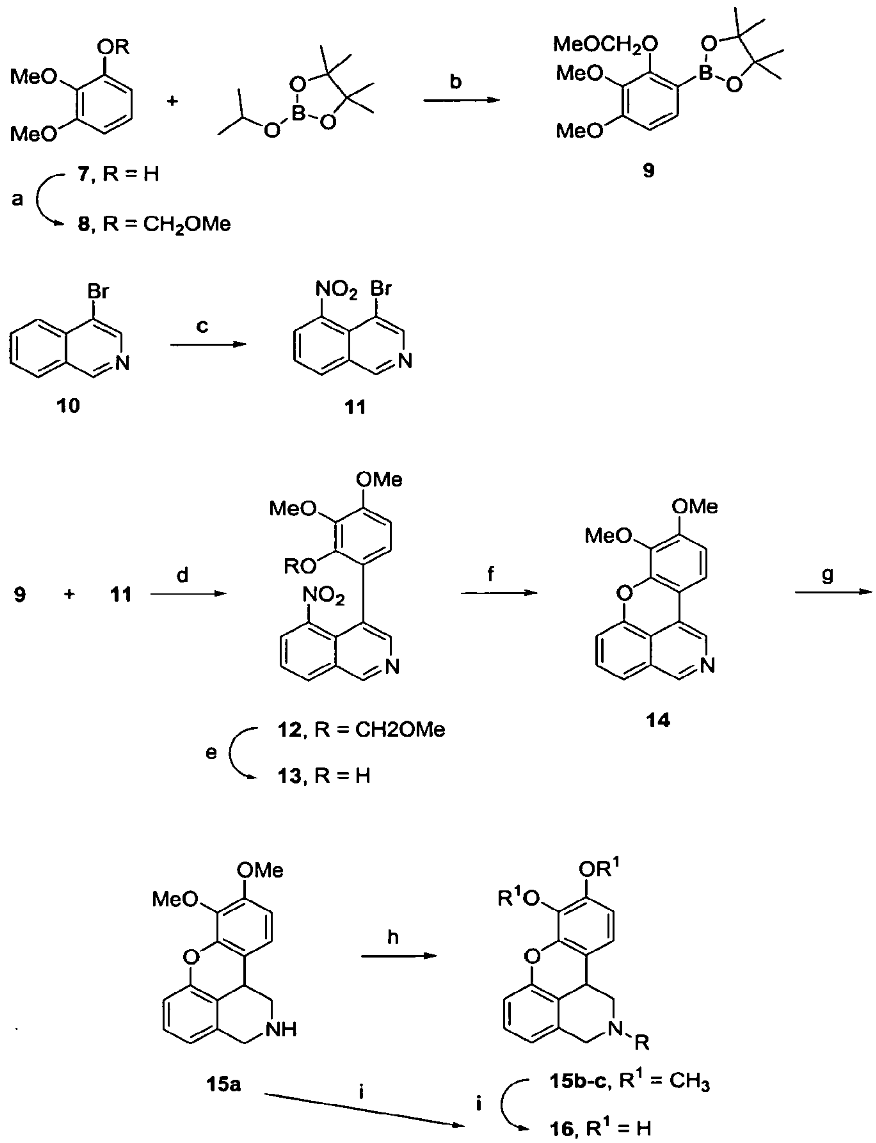
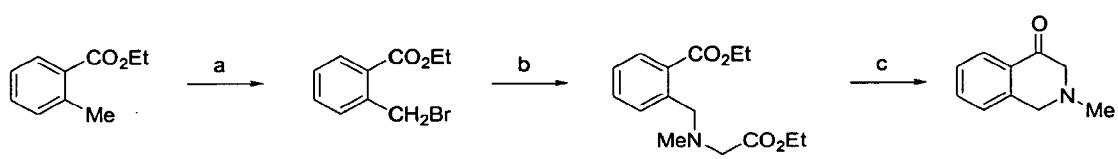
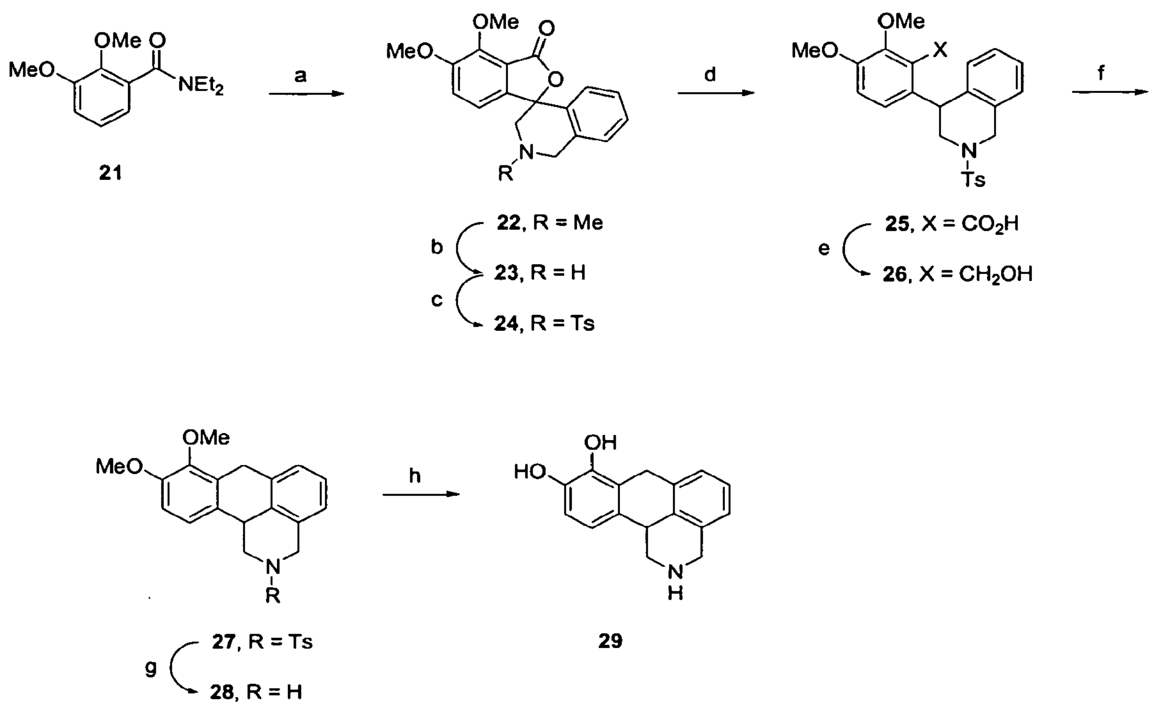


Fig. 2



17 18 19 20

Fig. 3



OMe
MeO
NEt2
21
a
22, R = Me
b
23, R = H
c
24, R = Ts
d
X
N
Ts
25, X = CO2H
e
26, X = CH2OH
f
27, R = Ts
g
28, R = H
h
OH
HO
29

Fig. 4